

Welcome to STN International! Enter x:x

LOGINID:sssptal600rxa

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	Jun 03	New e-mail delivery for search results now available
NEWS	4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	7	Sep 03	JAPIO has been reloaded and enhanced
NEWS	8	Sep 16	Experimental properties added to the REGISTRY file
NEWS	9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	11	Oct 24	BEILSTEIN adds new search fields
NEWS	12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	13	Nov 18	DKILIT has been renamed APOLLIT
NEWS	14	Nov 25	More calculated properties added to REGISTRY
NEWS	15	Dec 04	CSA files on STN
NEWS	16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS	17	Dec 17	TOXCENTER enhanced with additional content
NEWS	18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS	20	Feb 13	CANCERLIT is no longer being updated
NEWS	21	Feb 24	METADEX enhancements
NEWS	22	Feb 24	PCTGEN now available on STN
NEWS	23	Feb 24	TEMA now available on STN
NEWS	24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS	25	Feb 26	PCTFULL now contains images
NEWS	26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS	27	Mar 20	EVENTLINE will be removed from STN
NEWS	28	Mar 24	PATDPAFULL now available on STN
NEWS	29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS	30	Apr 11	Display formats in DGENE enhanced
NEWS	31	Apr 14	MEDLINE Reload
NEWS	32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS	33	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS	34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS	35	Apr 28	RDISCLOSURE now available on STN
NEWS	36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS	37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS	38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS	39	May 16	CHEMREACT will be removed from STN
NEWS	40	May 19	Simultaneous left and right truncation added to WSCA
NEWS	41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS	42	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS	43	Jun 06	PASCAL enhanced with additional data

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP);  
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
NEWS HOURS STN Operating Hours Plus Help Desk Availability  
NEWS INTER General Internet Information  
NEWS LOGIN Welcome Banner and News Items  
NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that  
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result in loss of user privileges and other penalties.

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

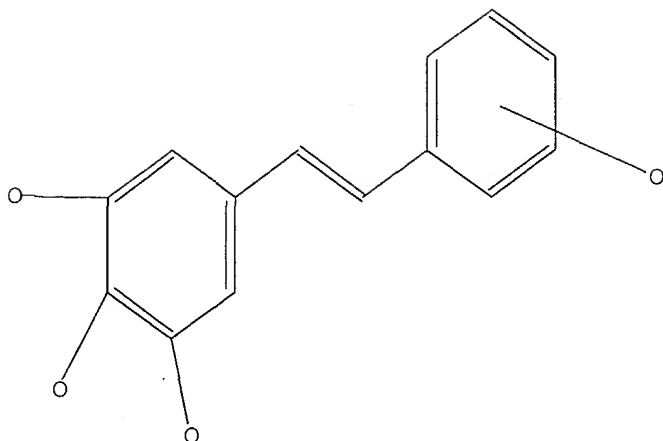
Uploading 10049248.str

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 08:08:48 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 133 TO ITERATE

100.0% PROCESSED 133 ITERATIONS  
SEARCH TIME: 00.00.01

41 ANSWERS

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 1969 TO 3351  
PROJECTED ANSWERS: 435 TO 1203

L2 41 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 08:08:52 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 2301 TO ITERATE

100.0% PROCESSED 2301 ITERATIONS  
SEARCH TIME: 00.00.01

675 ANSWERS

L3 675 SEA SSS FUL L1

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
148.15	148.36

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003  
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L4 407 L3

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.42	148.78

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003  
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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6  
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

Uploading 10049248.str

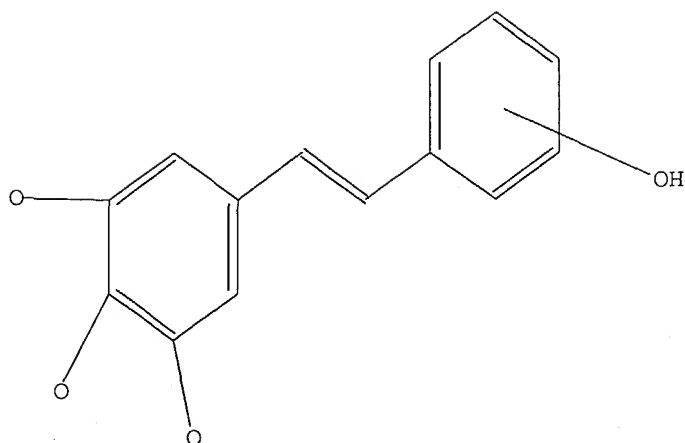
L5 STRUCTURE UPLOADED

=> d

L5 HAS NO ANSWERS

L5 STR





Structure attributes must be viewed using STN Express query preparation.

=> d his

(FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003)

FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

L1 STRUCTURE UPLOADED

L2 41 S L1

L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003

L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

L5 STRUCTURE UPLOADED

=> s l5 subset=l3 full

FULL SUBSET SEARCH INITIATED 08:09:42 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 675 TO ITERATE

100.0% PROCESSED 675 ITERATIONS

108 ANSWERS

SEARCH TIME: 00.00.01

L6 108 SEA SUB=L3 SSS FUL L5

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

35.30

184.08

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 16

L7 218 L6

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.42

184.50

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003  
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DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

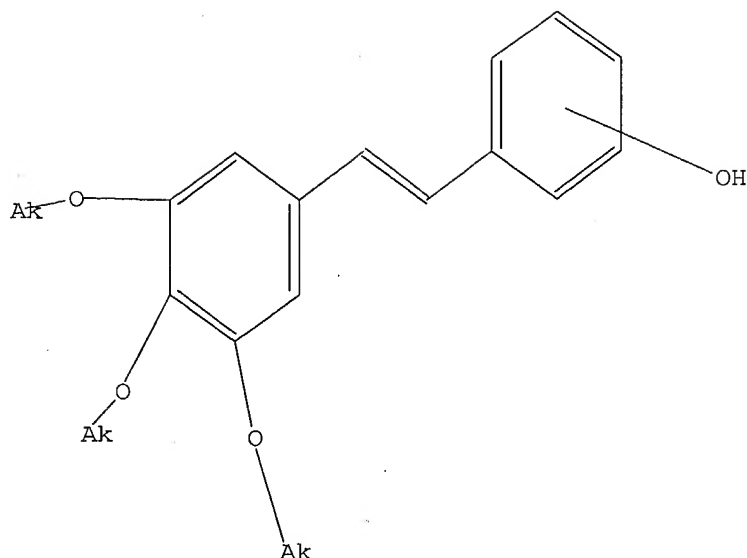
Uploading 10049248.str

L8 STRUCTURE UPLOADED

=> d

L8 HAS NO ANSWERS

L8 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l8 subset=l6 full

FULL SUBSET SEARCH INITIATED 08:10:32 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 108 TO ITERATE

100.0% PROCESSED 108 ITERATIONS

76 ANSWERS

SEARCH TIME: 00.00.01

L9 76 SEA SUB=L6 SSS FUL L8

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

35.30

219.80

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25

FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate

substance identification.

=> s 19

L10 169 L9

=>

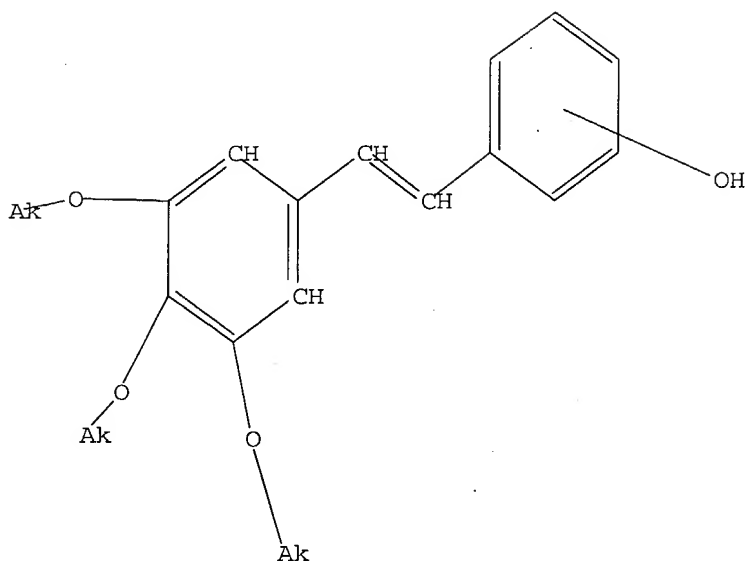
Uploading 10049248.str

L11 STRUCTURE UPLOADED

=> d

L11 HAS NO ANSWERS

L11 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l11 subset=19 full

**REGISTRY INITIATED**

Substance data SEARCH and crossover from CAS REGISTRY in progress...

Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

FULL SUBSET SEARCH INITIATED 08:11:31 FILE 'REGISTRY'  
FULL SUBSET SCREEN SEARCH COMPLETED - 76 TO ITERATE

100.0% PROCESSED 76 ITERATIONS  
SEARCH TIME: 00.00.01

60 ANSWERS

L12 60 SEA SUB=L9 SSS FUL L11

SUBSET IS IGNORED AS A SCOPE FOR THIS SEARCH

Page 9 06/19/2003

L13 166 L12

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.42	256.35

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003  
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DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> s l11 subset=19 full

FULL SUBSET SEARCH INITIATED 08:11:41 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 76 TO ITERATE

100.0% PROCESSED 76 ITERATIONS  
SEARCH TIME: 00.00.01

60 ANSWERS

L14 60 SEA SUB=L9 SSS FUL L11

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
35.30	291.65

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003  
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l14

L15 166 L14

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.42

292.07

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003

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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

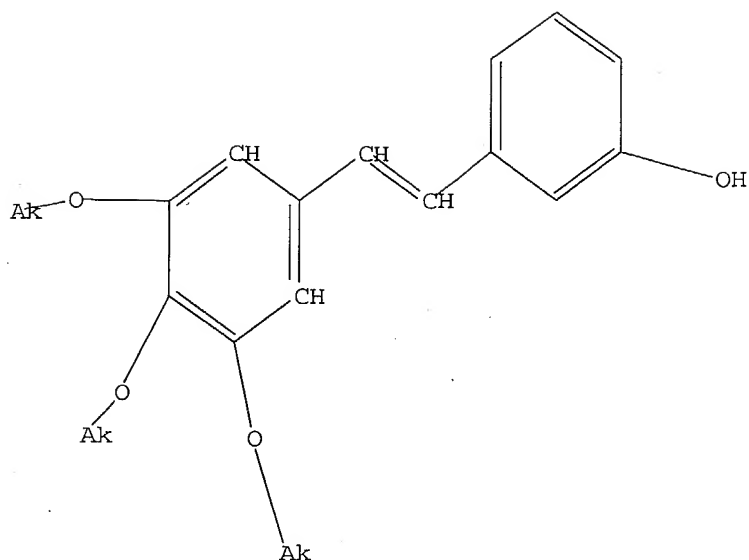
Uploading 10049248.str

L16 STRUCTURE UPLOADED

=> d

L16 HAS NO ANSWERS

L16 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l16 subset=l14 full

FULL SUBSET SEARCH INITIATED 08:12:32 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 60 TO ITERATE

100.0% PROCESSED 60 ITERATIONS

46 ANSWERS

SEARCH TIME: 00.00.01

L17 46 SEA SUB=L14 SSS FUL L16

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

35.30

327.37

FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25

FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate

substance identification.

=> s l17

L18 160 L17

=>

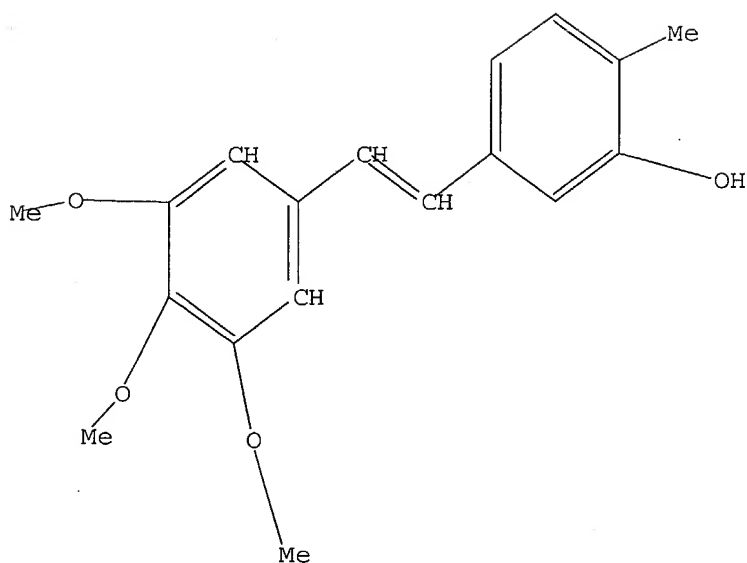
Uploading 10049248.str

L19 STRUCTURE UPLOADED

=> d

L19 HAS NO ANSWERS

L19 STR



Structure attributes must be viewed using STN Express query preparation.

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE TOTAL

ENTRY SESSION

FULL ESTIMATED COST

0.83 328.20

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003

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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d his

(FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003)

FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

L1 STRUCTURE UPLOADED  
L2 41 S L1  
L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003

L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

L5 STRUCTURE UPLOADED  
L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003

L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003

L8 STRUCTURE UPLOADED  
L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003

L10 169 S L9  
L11 STRUCTURE UPLOADED  
S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

L12 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003

L13 166 S L12 SUBSET=L9 FULL

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003

L14 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003

L15 166 S L14

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003

L16 STRUCTURE UPLOADED  
L17 46 S L16 FULL SUB=L14

FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003

L18 160 S L17  
L19 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003

=> s l19 subset=l117

LL17 IS NOT A VALID L#

L-numbers must be in the range L1-L999.

ENTER SUBSET L# OR (END):l17

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ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):full

FULL SUBSET SEARCH INITIATED 08:13:56 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS

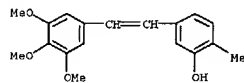
2 ANSWERS

SEARCH TIME: 00.00.01

L20 2 SEA SUB=L17 SSS FUL L19

=> d scan

L20 2 ANSWERS REGISTRY COPYRIGHT 2003 ACS  
IN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI)  
MF C18 H20 O4

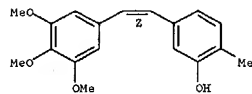


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L20 2 ANSWERS REGISTRY COPYRIGHT 2003 ACS  
IN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI)  
MF C18 H20 O4

Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

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=> fil caplus  
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
35.30	363.50

FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003  
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 120

L21 3 L20

=> d ibib abs hitstr 1-3

L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:487508 CAPLUS

DOCUMENT NUMBER: 137:47052

TITLE: Preparation of substituted stilbenes as antitumor agents

INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John

PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK

SOURCE: PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

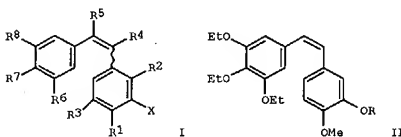
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002016228	A5	20020701	AU 2002-16228	20011220
PRIORITY APPLN. INFO.: GB 2000-31262 A 20001221				
GB 2001-235 A 20010105				
WO 2001-GB5702 W 20011220				

OTHER SOURCE(S): MARPAT 137:47052

GI



AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO<sub>2</sub>, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH<sub>2</sub>, O-aryl, O-heteroaryl; R<sub>1</sub> = alkyl, CHO, alkoxy, amino, SR, CF<sub>3</sub>, halogen; R<sub>2</sub>, R<sub>3</sub> = H, alkyl, alkoxy, OH, amino, thio, CF<sub>3</sub>, halogen; R<sub>4</sub>, R<sub>5</sub> = H, alkyl, CH<sub>2</sub>NHCO<sub>2</sub>R, CH<sub>2</sub>CONHR; R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> = H, alkyl, alkoxy; zigzag bond

L21 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:137169 CAPLUS

DOCUMENT NUMBER: 134:178403

TITLE: Preparation and use of cis-stilbenes with vascular damaging activity

INVENTOR(S): Davis, Peter David

PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK

SOURCE: PCT Int. Appl., 17 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

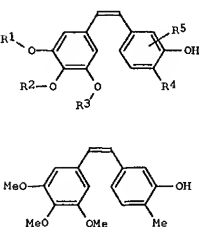
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809
PRIORITY APPLN. INFO.: GR 1999-18912 A 19990812				
WO 2000-GB3067 W 20000809				

OTHER SOURCE(S): MARPAT 134:178403

GI



AB Compds. of formula I [wherein; R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are alkyl; R<sub>4</sub> is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)

= cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-O-t-butylidimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene (II; R = TBSMS) which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC<sub>50</sub> = 0.018  $\mu$ M against MTT (K562) cell line.

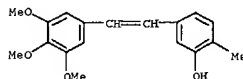
IT 438534-68-OP

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of substituted stilbenes as antitumor agents)

RN 438534-68-0 CAPLUS

CN Phenol, 2-methyl-5-[(2-(3,4,5-trimethoxyphenyl)ethenyl)- (9CI) (CA INDEX NAME)



L21 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)

R<sub>5</sub> is H, alkoxy, alkyl, alkylthio, hydroxy or halo] are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butylidimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by retn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.

IT 288585-59-1P, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

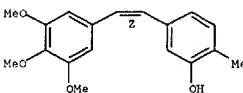
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. and use of stilbenes with vascular damaging activity)

RN 288585-59-1 CAPLUS

CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



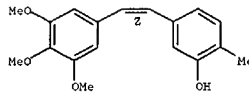
L21 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:592548 CAPLUS  
DOCUMENT NUMBER: 133:177486  
TITLE: Preparation of substituted stilbene compounds with  
vascular damaging activity  
INVENTOR(S): Davis, Peter David  
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
SOURCE: PCT Int. Appl., 31 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1154767	A1	20011121	EP 2000-903824	20000215
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPLN. INFO.:			GB 1999-3403	A 19990216
			WO 2000-GB503	W 20000215

OTHER SOURCE(S): MARPAT 133:177486  
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub> to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SAs tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.  
IT 2005585-59-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of substituted stilbene compds. with vascular damaging activity)  
RN 2005585-59-1 CAPLUS  
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L21 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Page 19 06/19/2003

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FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

L1 STRUCTURE UPLOADED  
L2 41 S L1  
L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003

L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

L5 STRUCTURE UPLOADED  
L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003

L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003

L8 STRUCTURE UPLOADED  
L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003

L10 169 S L9  
L11 STRUCTURE UPLOADED  
S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

L12 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003

L13 166 S L12 SUBSET=L9 FULL

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003

L14 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003

L15 166 S L14

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003

L16 STRUCTURE UPLOADED  
L17 46 S L16 FULL SUB=L14

FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003

L18 160 S L17  
L19 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003

L20 2 S L19 SUB=L17 FULL

FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003

L21 3 S L20

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE  
ENTRY

TOTAL  
SESSION

Page 20 06/19/2003

FULL ESTIMATED COST	14.86	378.36
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.95	-1.95

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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6  
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

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Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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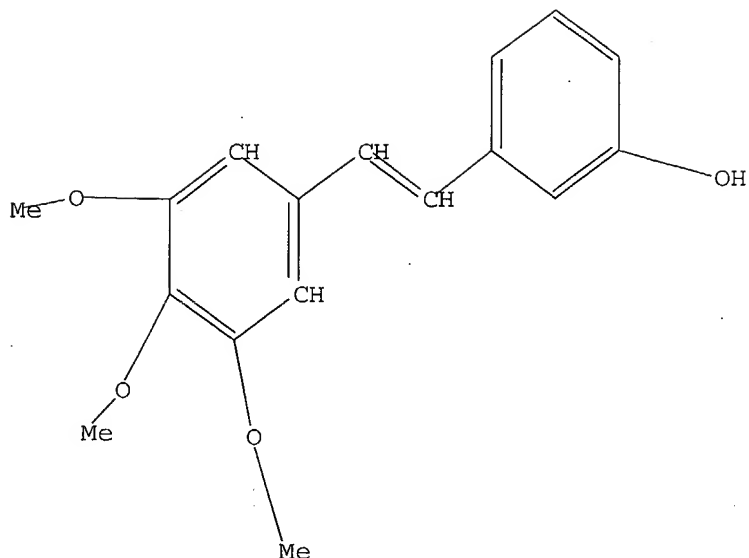
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L22 HAS NO ANSWERS

L22 STR





Structure attributes must be viewed using STN Express query preparation.

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FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

L1 STRUCTURE UPLOADED

L2 41 S L1

L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003

L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

L5 STRUCTURE UPLOADED

L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003

L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003

L8 STRUCTURE UPLOADED

L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003

L10 169 S L9

L11 STRUCTURE UPLOADED

S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

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L12 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003  
L13 166 S L12 SUBSET=L9 FULL

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003  
L14 60 S L11 FULL SUB=L9

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L15 166 S L14

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003  
L16 STRUCTURE UPLOADED  
L17 46 S L16 FULL SUB=L14

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L18 160 S L17  
L19 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003  
L20 2 S L19 SUB=L17 FULL

FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003  
L21 3 S L20

FILE 'REGISTRY' ENTERED AT 08:15:36 ON 19 JUN 2003  
L22 STRUCTURE UPLOADED

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FULL SUBSET SEARCH INITIATED 08:22:01 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 46 TO ITERATE

100.0% PROCESSED 46 ITERATIONS

35 ANSWERS

SEARCH TIME: 00.00.01

L23 35 SEA SUB=L17 SSS FUL L22

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

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417.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

0.00

-1.95

FILE 'CAPLUS' ENTERED AT 08:22:05 ON 19 JUN 2003

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 123

L24 157 L23

=>

Uploading 10049248.str

L25 STRUCTURE UPLOADED

=> fil reg.

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.83	418.49
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-1.95

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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6  
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

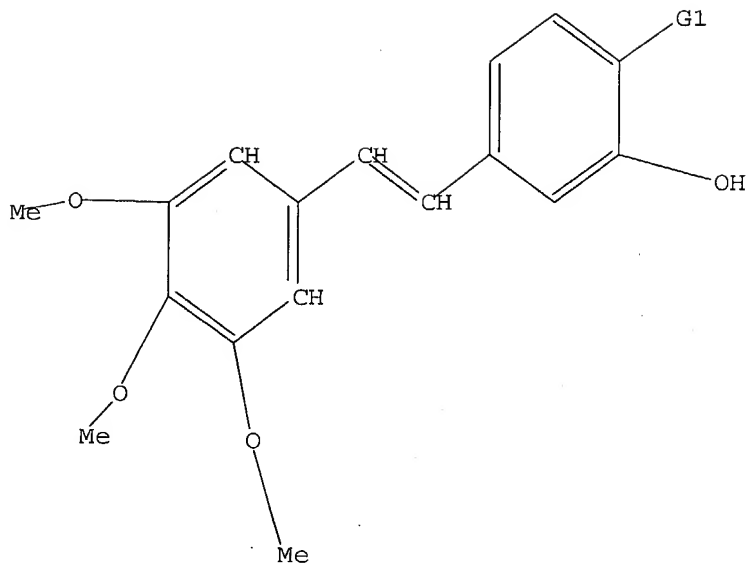
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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L25 HAS NO ANSWERS  
L25 STR



G1 C,S,X

Structure attributes must be viewed using STN Express query preparation.

=> d his

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FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003

L1 STRUCTURE UPLOADED

L2 41 S L1

L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003

L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

L5 STRUCTURE UPLOADED

L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003

L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003

L8 STRUCTURE UPLOADED

L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003

L10 169 S L9

L11 STRUCTURE UPLOADED

S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

Page 25 06/19/2003

L12 60 S L11 FULL SUB=L9  
FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003  
L13 166 S L12 SUBSET=L9 FULL  
FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003  
L14 60 S L11 FULL SUB=L9  
FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003  
L15 166 S L14  
FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003  
L16 STRUCTURE UPLOADED  
L17 46 S L16 FULL SUB=L14  
FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003  
L18 160 S L17  
L19 STRUCTURE UPLOADED  
FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003  
L20 2 S L19 SUB=L17 FULL  
FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003  
L21 3 S L20  
FILE 'REGISTRY' ENTERED AT 08:15:36 ON 19 JUN 2003  
L22 STRUCTURE UPLOADED  
L23 35 S L22 SUB=L17 FULL  
FILE 'CAPLUS' ENTERED AT 08:22:05 ON 19 JUN 2003  
L24 157 S L23  
L25 STRUCTURE UPLOADED  
FILE 'REGISTRY' ENTERED AT 08:23:33 ON 19 JUN 2003

=> s l25 subset=l23  
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FULL SUBSET SEARCH INITIATED 08:23:54 FILE 'REGISTRY'  
FULL SUBSET SCREEN SEARCH COMPLETED - 8 TO ITERATE

100.0% PROCESSED 8 ITERATIONS 6 ANSWERS  
SEARCH TIME: 00.00.01

L26 6 SEA SUB=L23 SSS FUL L25

=> fil caplus  
COST IN U.S. DOLLARS

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

CA SUBSCRIBER PRICE

SINCE FILE	TOTAL
ENTRY	SESSION
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0.00	-1.95

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L27 5 L26

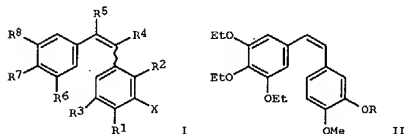
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## L27 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:487508 CAPLUS  
 DOCUMENT NUMBER: 137:47052  
 TITLE: Preparation of substituted stilbenes as antitumor agents  
 INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hopworth, Lucy Annette; Butler, John  
 PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK  
 SOURCE: PCT Int. Appl., 76 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, US, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002016228	A5	20020701	AU 2002-16228	20011220
PRIORITY APPLN. INFO.: AU 2000-31262 A 20011220 GB 2001-295 A 20010105 WO 2001-GB5702 W 20011220				

OTHER SOURCE(S): MARPAT 137:47052  
 GI



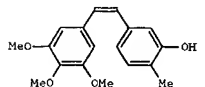
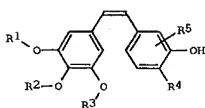
AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO<sub>2</sub>, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH<sub>2</sub>, O-aryl, O-heteroaryl; R<sub>1</sub> = alkyl, CHO, alkoxy, amino, SR, CF<sub>3</sub>, halogen; R<sub>2</sub>, R<sub>3</sub> = H, alkyl, alkoxy, OH, amino, thio, CF<sub>3</sub>, halogen; R<sub>4</sub>, R<sub>5</sub> = H, alkyl, CH<sub>2</sub>NHCO<sub>2</sub>R, CH<sub>2</sub>CONH<sub>2</sub>; R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> = H, alkyl, alkoxy; zigzag bond

## L27 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:137169 CAPLUS  
 DOCUMENT NUMBER: 134:178403  
 TITLE: Preparation and use of cis-stilbenes with vascular damaging activity  
 INVENTOR(S): Davis, Peter David  
 PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
 SOURCE: PCT Int. Appl., 17 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
JF 2003507356	T2	20030225	JF 2001-516880	20000809
PRIORITY APPLN. INFO.: GB 1999-18912 A 19990812 WO 2000-GB3067 W 20000809				

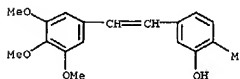
OTHER SOURCE(S): MARPAT 134:178403  
 GI



AB Compds. of formula I [wherein: R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are alkyl; R<sub>4</sub> is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

## L27 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)

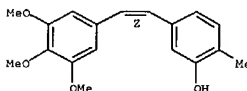
= cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-O-t-butylidimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC<sub>50</sub> = 0.018  $\mu$ M against MTT(K562) cell line.  
 IT 438534-68-0P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of substituted stilbenes as antitumor agents)  
 RN 438534-68-0 CAPLUS  
 CN Phenol, 2-methyl-5-[(2-(3,4,5-trimethoxyphenyl)ethenyl)- (9CI) (CA INDEX NAME)]



## L27 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)

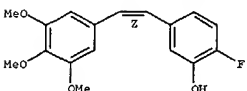
R<sub>5</sub> is H, alkoxy, alkyl, alkylthio, hydroxy or halo are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butylidimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by reduct. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.  
 IT 288585-59-1P, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (prepn. and use of stilbenes with vascular damaging activity)  
 RN 288585-59-1 CAPLUS  
 CN Phenol, 2-methyl-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



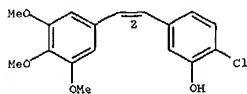
IT 326850-81-1P, (Z)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-82-2P, (Z)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-83-3P, (Z)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. and use of stilbenes with vascular damaging activity)  
 RN 326850-81-1 CAPLUS  
 CN Phenol, 2-fluoro-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



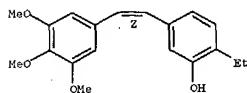
RN 326850-82-2 CAPLUS  
 CN Phenol, 2-chloro-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L27 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)  
Double bond geometry as shown.

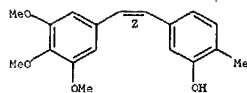


RN 326850-83-3 CAPLUS  
CN Phenol, 2-ethyl-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:592548 CAPLUS  
DOCUMENT NUMBER: 133:177486  
TITLE: Preparation of substituted stilbene compounds with  
vascular damaging activity  
INVENTOR(S): Davis, Peter David  
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
SOURCE: PCT Int. Appl., 31 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, EF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216 WO 2000-GB503 W 20000215				

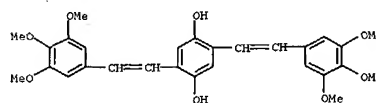
OTHER SOURCE(S): MARPAT 133:177486  
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyl)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CH<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub> to give (Z)-1-[4-methoxy-3-(N-.omega.-nitroarginyl)-2-(3,4,5-trimethoxyphenyl)ethene]. The latter at 50 mg/kg i.p. in mice bearing C<sub>57</sub> or S<sub>18</sub> tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.  
IT 288585-59-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of substituted stilbene compds. with vascular damaging activity)  
RN 288585-59-1 CAPLUS  
CN Phenol, 2-methyl-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
INDEX NAME)

Double bond geometry as shown.

L27 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:351266 CAPLUS  
DOCUMENT NUMBER: 132:345122  
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors  
INVENTOR(S): Huyberechts, Guido; Jordens, Sven  
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instituut Antwerpen  
SOURCE: Eur. Pat. Appl., 18 pp.  
CODEN: EPXNDW  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117 US 1999-122211P P 19990301				

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.  
IT 270069-97-1P, alkyl deriva.  
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)  
RN 270069-97-1 CAPLUS  
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L27 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:351265 CAPLUS

DOCUMENT NUMBER: 132:345121

TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors

INVENTOR(S): Huyberechts, Guido; Jordens, Sven

PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen

SOURCE: Eur. Pat. Appl., 14 pp.

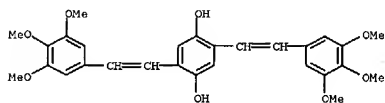
DOCUMENT TYPE: CODEN: EFXNDW

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002048751	A1	20020425	US 1999-441118	19991117
PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117				
US 1999-122211P P 19990301				
AB	An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.			
IT	270069-97-1DP, alkyl derivative.			
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)				
(as oligomer) sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)				
RN	270069-97-1 CAPLUS			
CN	1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)			



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)

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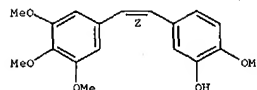
L24 ANSWER 1 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:434278 CAPLUS  
 TITLE: Combination bacteriolytic therapy for the treatment of tumors  
 INVENTOR(S): Dang, Long; Kinzler, Kenneth W.; Vogelstein, Bert  
 PATENT ASSIGNEE(S): The Johns Hopkins University, USA  
 SOURCE: PCT Int. Appl., 33 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045153	A1	20030605	WO 2002-US37509	20021121
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, BR, BU, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPL. INFO.: US 2001-331786 P 20011121  
 AB Current chemotherapeutic approaches for cancer are in part limited by the inability of drugs to destroy neoplastic cells within poorly vascularized compartments of tumors. We have here systematically assessed anaerobic bacteria for their capacity to grow expansively within avascular compartments of transplanted tumors. Among 26 different strains tested, one (*Clostridium novyi*) appeared particularly promising. We created a strain of *C. novyi* devoid of its lethal toxin (*C. novyi*-NT) and showed that i.v. injected *C. novyi*-NT spores germinated within the avascular regions of tumors in mice and destroyed surrounding viable tumor cells. When *C. novyi*-NT spores were administered together with conventional chemotherapeutic drugs, extensive hemorrhagic necrosis of tumors often developed within 24 h, resulting in significant and prolonged anti-tumor effects. This strategy, called combination bacteriolytic therapy (COBALT), has the potential to add a valuable dimension to the treatment of cancer.  
 IT 117048-59-6, combretastatin A-4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination bacteriolytic therapy for treatment of tumors)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

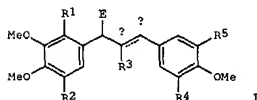
L24 ANSWER 1 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 2 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:376801 CAPLUS  
 DOCUMENT NUMBER: 138:385212  
 TITLE: Combretastatin A4 derivatives having antineoplastic activity  
 INVENTOR(S): Lawrence, Nicholas James; Hadfield, John Anthony; McGown, Alan Thomson; Butler, John; Ducki, Sylvie; Rennison, David; Woo, Melki  
 PATENT ASSIGNEE(S): Paterson Institute for Cancer Research, UK; University of Manchester Institute of Science and Technology  
 SOURCE: PCT Int. Appl., 69 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040077	A1	20030515	WO 2002-GB5055	20021108
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, BR, BU, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPL. INFO.: GB 2001-26889 A 20011108  
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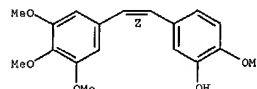


AB Compds., such as I [E = oxo, OH; R1, R2 = H, alkoxy; R3 = H, CH2NH2, CH2OH, alkyl, alkylaminomethyl, etc.; R4 = H, halogen; R5 = H, alkoxy, halogen; .alpha.,.beta.-bond = single or double], were prepd. and were designed to mimic the activity of combretastatin A-4 based on chalcone, avone, or indanone structures, or involving benzquinone or quinone rings. These compds. are useful for the treatment of cancer or a condition involving abnormal proliferation of vasculature, diabetic retinopathy, psoriasis or endometriosis. Thus, MW 47 I [E = oxo, R1 = R3 = R4 = H, R2 = OMe, R5 = NO2, .alpha.,.beta.-bond = (E)-double] was prepd. with 61% yield by reaction of 3,4,5-trimethoxyacetophenone and 4-methoxy-3-nitrobenzaldehyde using a sodium hydroxide water soln. in MeOH. The anti-cancer activity of exemplified compds. was demonstrated in a range of in vitro and in vivo assays.  
 IT 117048-59-6DP, Combretastatin A4, analogs  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

L24 ANSWER 2 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

(Therapeutic use); BIOL (Biological study); PREF (Preparation); USES (Uses)  
 (prepn. of combretastatin A4 analogs having antineoplastic activity)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

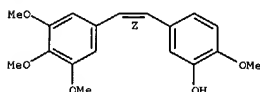


L24 ANSWER 5 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:356182 CAPLUS  
 DOCUMENT NUMBER: 138:348759  
 TITLE: Indolylquinolinone derivative tyrosine kinase inhibitors, preparation thereof, and therapeutic use  
 INVENTOR(S): Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 82 pp.  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037252	A2	20030508	WO 2002-US34379	20021025
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, NO, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-339075P P 20011030  
 OTHER SOURCE(S): MARPAT 138:348759  
 AB The invention provides indolylquinolinone compds. which inhibit, regulate, and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age-related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. Prepn. of selected compds. is described.  
 IT 117048-59-6, Combiatastatin A-4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (indolylquinolinone deriv. tyrosine kinase inhibitors, prepn., therapeutic use, and use with other agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

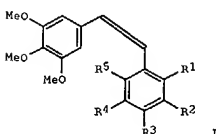
Double bond geometry as shown.



L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:334852 CAPLUS  
 DOCUMENT NUMBER: 138:353746  
 TITLE: Preparation of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization.  
 INVENTOR(S): Chaplin, David J.; Garner, Charles Manly, III; Kane, Robert Ronald; Pinney, Kevin G.; Prezioso, Joseph Anthony  
 PATENT ASSIGNEE(S): Origene, Inc., USA  
 SOURCE: PCT Int. Appl., 56 pp.  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035008	A2	20030501	WO 2002-US34497	20021028
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, NO, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-337348P P 20011026  
 OTHER SOURCE(S): MARPAT 138:353746  
 GI

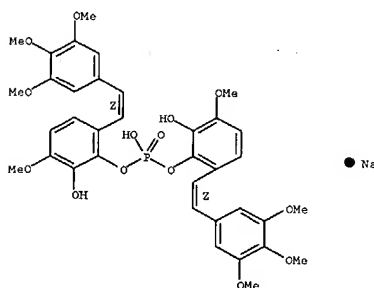


AB Title compds. [I: R1, R4, R5 = H, OH, alkoxy, amino, NO2, N3, halo, phosphate ester salt; R2 = H, OH, alkoxy, amino, NO2, amino, phosphate ester salt]; R1R2 = atoms to form a ring; R3 = H, alkoxy, phosphate ester salt], were prepd. Thus, 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (prepn. given) in THF was treated with BuLi in THF at -15.degree.; the mixt. was stirred 30 min. at room temp. followed by addn. of 2-(tert-butylidimethylsilyloxy)-3-bromo-4-methoxybenzaldehyde (prepn. given) and stirring for 3h to give 78.7% E,Z-stilbene deriv., which was stirred with KF and HBr in DMF to give (Z)-2'-hydroxy-3'-bromo-3,4,4',5'-tetramethoxystilbene. Tested I at 100 mg/kg i.p. in mice bearing MHEC-57 hemangioendothelioma tumors gave 41-90% blood flow shutdown.  
 IT 519060-02-7P

L24 ANSWER 5 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

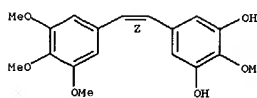
L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (claimed compd., prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)  
 RN 519060-02-7 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, 1,1'-(hydrogen phosphate), monosodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 519060-08-3P 519060-09-4P 519060-13-OP  
 519060-14-1P 519060-17-4P 519060-21-OP  
 519060-24-3P 519060-27-6P 519060-28-7P  
 519060-29-8P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)  
 RN 519060-08-3 CAPLUS  
 CN 1,3-Benzenediol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



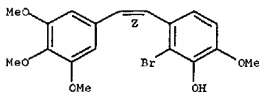
RN 519060-09-4 CAPLUS  
 CN Phenol, 2-bromo-6-methoxy-3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]-

L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

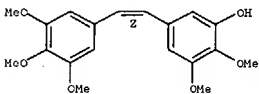
RN 519060-13-0 CAPLUS

CN Phenol, 2,3-dimethoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



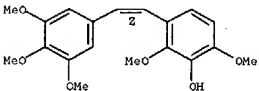
Double bond geometry as shown.



RN 519060-14-1 CAPLUS

CN Phenol, 2,6-dimethoxy-3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 519060-17-4 CAPLUS

CN 1,2-Benzenediol, 3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

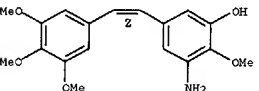


L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

RN 519060-28-7 CAPLUS

CN Phenol, 3-amino-2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

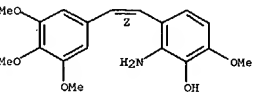
Double bond geometry as shown.



RN 519060-29-8 CAPLUS

CN Phenol, 2-amino-6-methoxy-3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 117048-59-6, Combretastatin A4.

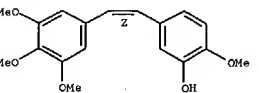
RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)

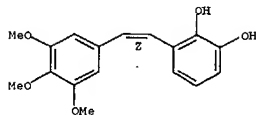
RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



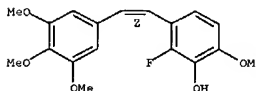
L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 519060-21-0 CAPLUS

CN Phenol, 2-fluoro-6-methoxy-3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

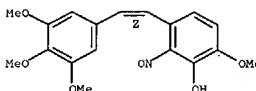
Double bond geometry as shown.



RN 519060-24-3 CAPLUS

CN Phenol, 6-methoxy-2-nitroso-3-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

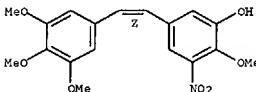
Double bond geometry as shown.



RN 519060-27-6 CAPLUS

CN Phenol, 2-methoxy-3-nitro-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 7 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:282298 CAPLUS

DOCUMENT NUMBER: 138:297698

TITLE: Somatostatin or bombesin analog conjugates, and therapeutic and diagnostic uses thereof

INVENTOR(S): Coy, David H.; Fuselier, Joseph A.; Murphy, William A.; Sun, Lichun

PATENT ASSIGNEE(S): The Administrators of the Tulane Educational Fund, USA

SOURCE: PCT Int. Appl., 86 pp.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003028527	A2	20030410	WO 2002-US30143	20020920

W	AE	AG	AL	AM	AT	AU	AZ	BA	BB	BG	BR	BY	BZ	CA	CH	CN
CO	CR	CU	CZ	DE	DK	DM	DZ	EC	EE	ES	FI	GB	GD	GE	GH	GM
HR	HU	ID	IL	IN	IS	JP	KE	KG	KP	KR	KZ	LC	LK	LR	LS	LT
LU	LV	MA	MD	MG	MK	MN	MW	MX	MZ	NO	NZ	OM	PH	PL	PT	RO
RU	SD	SE	SG	SI	SK	SL	TJ	TH	TN	TR	TT	TZ	UA	UG	US	UZ
VC	VN	YU	ZA	ZM	ZW	AM	AE	EV	XG	XZ	MD	RU	TJ	TM	RW	GH
GM	KE	LS	MW	MZ	SD	SL	SZ	T2	UG	ZM	ZW	AT	BE	BG	CH	CY
CZ	DE	DK	EE	ES	FI	FR	GB	GR	IE	IT	LU	MC	NL	PT	SE	SK
TR	BF	BJ	CF	CG	CI	CM	GA	GN	GQ	GW	ML	MR	NE	SN	TD	TG

PRIORITY APPLN. INFO.: MARPAT 138:297698

OTHER SOURCE(S): The invention discloses somatostatin and bombesin analog conjugates and uses thereof for targeting compds. useful for detection, diagnosis, and treatment of diseases. The peptide agents of the invention include XYZQ (X = cytotoxic agent, detectable label, etc., or is omitted; Y = peptide increasing hydrophilic biodistribution of agent, hydrophilic polymer including linker for X, omitted; Z = linking peptide; Q = peptide with biol. activity, e.g. somatostatin peptide).

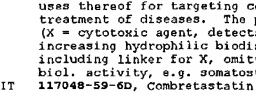
IT 117048-59-6D, Combretastatin A4, peptide conjugates

RL: DGN (Diagnostic use); PAC (Pharmacological activity); PRF (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (somatostatin or bombesin analog conjugates, and therapeutic and diagnostic uses thereof)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



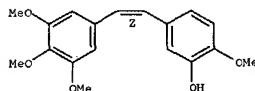
L24 ANSWER 8 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:261611 CAPLUS  
 DOCUMENT NUMBER: 138:292740  
 TITLE: p-Amidobenzyl ethers in drug delivery agents  
 INVENTOR(S): Senter, Peter D.; Toki, Brian E.  
 PATENT ASSIGNEE(S): Seattle Genetics, Inc., USA  
 SOURCE: PCT Int. Appl., 109 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003026577	A2	20030403	WO 2002-US30282	20020924
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003096743	A1	20030522	US 2001-963103	20010924
PRIORITY APPL. INFO.: US 2001-963103 A 20010924 US 2002-252947 A 20020923				

OTHER SOURCE(S): MARPAT 138:292740  
 AB Comps. [L-[An-Z-X-Ww]-D and B-[Z-X-Ww]-D, where D is a drug moiety, L is a ligand, B is a blocking group, A = acyl Z = amino acid or a peptide, X = aminobenzyl ether spacer group, W = optional second group, n = 0 or 1, and w = 0 or 1] and compts. of the compts. with carriers, diluents and/or excipients, and methods of delivery of the drugs are disclosed. Thus, etoposide was allowed to react with a peptide-contg. and the product obtained was shown to be very stable at pH 5.1 and 7.2 after 7 days.  
 IT 117048-59-6, Combretastatin A4  
 RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (amidobenzyl ethers as drug delivery agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 9 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:259780 CAPLUS  
 DOCUMENT NUMBER: 138:281082  
 TITLE: Methods for evaluating treatment efficacy on Kaposi's Sarcoma using angiogenesis associated gene marker  
 INVENTOR(S): Der Kuyll, Antoinette C.; Cornelissen, Marion  
 PATENT ASSIGNEE(S): Primagene Holding B.V., Neth.  
 SOURCE: Eur. Pat. Appl., 94 pp.  
 CODEN: EYXDXW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1298221	A1	20030402	EP 2001-203703	20010928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
EP 1225233	A2	20020724	EP 2002-75264	20020123
EP 1225233	A3	20030108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
WO 2002059558	A2	20020801	WO 2002-NL51	20020123
WO 2002059558	A3	20030109		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IL, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPL. INFO.: EP 2001-200228 A 20010123 EP 2001-203703 A 20010928 US 2001-325722 P 20010928				

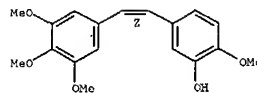
AB The invention provides a method for detg. whether a treatment is effective in changing the status of a certain set of target cells, such as a tumor, in a patient. This method implies obtaining a sample from a patient after initiation of a treatment, and detg. whether said sample comprises an expression product of at least one marker gene. Preferably, said sample is a blood sample. In one aspect, said expression product is expressed by a peripheral blood mononuclear cell. Said marker gene may be a gene involved in the generation, maintenance and/or breakdown of blood vessels (angiogenesis). A method of the invention is very suitable to det. within a few days if a certain treatment against Kaposi's Sarcoma is successful. Moreover, this method is suitable for detg. the presence of angiogenesis and/or tumor cells in a patient.

IT 117048-59-6, Combretastatin A4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (methods for evaluating treatment efficacy on Kaposi's Sarcoma using angiogenesis assoc. gene marker)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 8 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 9 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

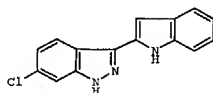
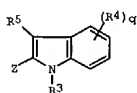


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:242336 CAPLUS  
 DOCUMENT NUMBER: 138:271678  
 TITLE: Preparation of substituted 2-(indazolyl)indoles as tyrosine kinase inhibitors  
 INVENTOR(S): Arrington, Kenneth L.; Fraley, Mark E.; Hanney, Barbara; Kim, Yuntae; Spencer, Keith L.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 117 pp.  
 DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: English  
 PATENT INFORMATION: 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024969	A1	20030327	WO 2002-US28779	20020910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-322075P P 20010914  
 OTHER SOURCE(S): MARPAT 138:271678  
 GI

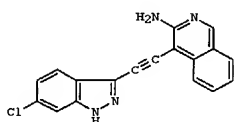
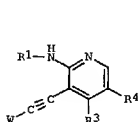


AB Title compds. I [Z = indazolyl, etc.; q = 1-3; R3 = H, (CO)0-1-alkyl, aryl, etc.; R4 = (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, etc.; R5 = H, (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, OH, etc.] are prepd. For instance, 6-chloroindazole (prepn. given) is converted to the corresponding 3-iodo deriv. (EtOH, Ag2SO4, I2), coupled to 1-(tert-butoxycarbonyl)indole-2-boronic acid (prepn. given) (dioxane, Pd(PPh3)4, LiCl, Na2CO3, 80 degree.) and the resulting coupled product deprotected (CH2Cl2, TFA, Me2S) to afford II. I inhibit, regulate and/or modulate tyrosine kinase signal transduction and are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases.  
 IT 117048-59-6, Combretastatin A-4  
 RI: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

L24 ANSWER 11 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:242301 CAPLUS  
 DOCUMENT NUMBER: 138:271674  
 TITLE: Preparation of substituted 3-amino-4-(indazolyl)isoquinolines as tyrosine kinase inhibitors  
 INVENTOR(S): Kim, Yuntae; Escudero, Irma P.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 84 pp.  
 DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: English  
 PATENT INFORMATION: 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024931	A1	20030327	WO 2002-US28775	20020910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

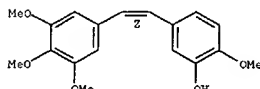
PRIORITY APPLN. INFO.: US 2001-322043P P 20010914  
 OTHER SOURCE(S): MARPAT 138:271674  
 GI



AB Title compds. I [R1 = H, alkyl; W = (hetero)aryl; R3-4 = H, (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, etc.] are prepd. For instance, 6-chloroindazole (prepn. given) is converted to the corresponding 3-iodo deriv. (EtOH, Ag2SO4, I2), coupled to 4-ethynylisoquinolin-3-ylamine (prepn. given from 3-aminoisoquinoline) (CH3CN, Pd(PPh3)4, CuI, Et3N, 80 degree., 3 h) to afford II. I inhibit, regulate and/or modulate tyrosine kinase signal transduction and are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases.  
 IT 117048-59-6, Combretastatin A-4  
 RI: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination pharmaceutical; substituted 3-amino-4-(indazolyl)isoquinolines as tyrosine kinase inhibitors)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 10 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 (combination pharmaceutical; prepn. of substituted 2-(indazolyl)indoles as tyrosine kinase inhibitors)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

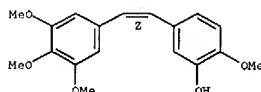
Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

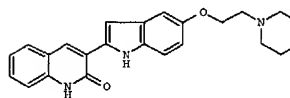
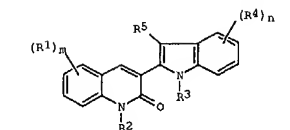


L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:202521 CAPLUS  
 DOCUMENT NUMBER: 138:238027  
 TITLE: Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors  
 INVENTOR(S): Pockham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 143 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020699	A2	20030313	WO 2002-US27114	20020826
WO 2003020699	A3	20030522		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, EF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-316123P P 20010830  
 GI

L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



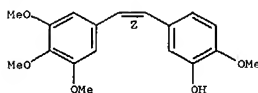
AB Title compds., including I (R groups undefined), were prepd. and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-((tert-butylidimethylsilyl)oxy)-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (prepn. of starting materials given) in the presence of Pd(PPh3)4 and K3PO4 in dioxane to give the protected 3-(2-indolyl)quinoline deriv. Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine, Bul.HCl and Cs2CO3 in DMF followed by reflux at 110.degree. in AcOH and H2O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 .mu.M - 5.0 .mu.M. Thus, I and compns. contg. I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT 117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination therapy; prepn. of (indolyl)quinolinones for treatment of cancer, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 13 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:202525 CAPLUS  
 DOCUMENT NUMBER: 138:243276  
 TITLE: Vascular implants containing combretastatin A-4 or combretastatin A-4 phosphate  
 INVENTOR(S): Knaudt, Stephan; Chaplin, David; Kuttler, Bernd; Lorenz, Guenter  
 PATENT ASSIGNEE(S): Orygene Inc., USA  
 SOURCE: PCT Int. Appl., 61 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020331	A1	20030313	WO 2002-EP9836	20020903
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, EF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10142897	A1	20030320	DE 2001-10142897	20010903
DE 10142881	A1	20030403	DE 2001-10142881	20010903

PRIORITY APPLN. INFO.: DE 2001-10142881 A 20010903  
 DE 2001-10142897 A 20010903

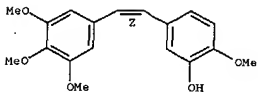
AB The invention relates to implants, in particular intracavernous or intravascular implants, preferably for the treatment or prophylaxis of coronary or peripheral vascular occlusion, strictures or stenosis, in particular for the prophylaxis of restenosis. The implants contain combretastatin A-4 or combretastatin A-4 phosphate that is chem. bonded in a covalent or non-covalent form or is in a phys. fixed form. Stents prepd. from alloys, polymers or their combination, also with alumina coating are treated with the alc. soln. of combretastatin A-4 or combretastatin A-4 phosphate under sterile condition. According to an other method combretastatin A-4 or combretastatin A-4 phosphate are included in a biodegradable polymer for coating. Other drugs can be added to the implants.

IT 117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (vascular implants contg. combretastatin A-4 or combretastatin A-4 phosphate)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 13 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

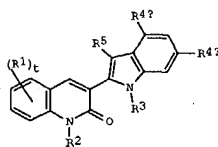


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 14 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:202476 CAPLUS  
 DOCUMENT NUMBER: 138:238026  
 TITLE: Preparation of indolylquinolinones as tyrosine kinase inhibitors with therapeutic uses  
 INVENTOR(S): Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.; Hartman, George D.; Arrington, Kenneth L.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 90 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020276	A1	20030313	WO 2002-US27161	20020826
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPL. INFO.:			US 2001-315897P P 20010830	
OTHER SOURCE(S):			MARPAT 138:238026	
GI				



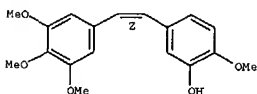
AB The present invention relates to indolylquinolinones (shown as I; variables defined below: e.g., 3-[6-[(4-methylpiperazin-1-yl)carboxyl]-1H-indol-2-yl]quinolin-2(1H)-one) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory

L24 ANSWER 14 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

diseases, and the like in mammals. For I: a = 0 or 1; b = 0 or 1; n = 0, 1, or 2; t = 1 or 2; R<sup>1</sup> and R<sup>5</sup> = H, (C<sub>0</sub>)aObC1-C10 alkyl, (C<sub>0</sub>)aObaryl, (C<sub>0</sub>)aObC2-C10 alkenyl, (C<sub>0</sub>)aObC2-C10 alkynyl, CO<sub>2</sub>H, halo, OH, ObC1-C6 perfluoroalkyl, (C<sub>0</sub>)aNR<sup>7</sup>R<sup>8</sup>, CN, (C<sub>0</sub>)aObC3-C8 cycloalkyl, and (C<sub>0</sub>)aObheterocyclyl. R<sup>2</sup> and R<sup>3</sup> = H, (C<sub>0</sub>)OaC1-C6 alkyl, (C<sub>0</sub>)Oaaryl, C1-C6 alkyl, SO<sub>2</sub>Ra, and aryl; R<sup>4</sup>a or R<sup>4</sup>b = H and the other = (C<sub>0</sub>)aObC1-C10 alkyl, (C<sub>0</sub>)aObaryl, (C<sub>0</sub>)aObC2-C10 alkenyl, (C<sub>0</sub>)aObC2-C10 alkynyl, CO<sub>2</sub>H, halo, OH, ObC1-C6 perfluoroalkyl, (C<sub>0</sub>)aNR<sup>7</sup>R<sup>8</sup>, CN, (C<sub>0</sub>)aObC3-C8 cycloalkyl, and (C<sub>0</sub>)aObheterocyclyl. R<sup>7</sup> and R<sup>8</sup> = H, (C<sub>0</sub>)ObC1-C10 alkyl, (C<sub>0</sub>)ObC3-C8 cycloalkyl, (C<sub>0</sub>)Obaryl, (C<sub>0</sub>)Obheterocyclyl, C1-C10 alkyl, aryl, C2-C10 alkenyl, C2-C10 alkynyl, heterocyclyl, C3-C8 cycloalkyl, SO<sub>2</sub>Ra, (C<sub>0</sub>)N(Rb)<sub>2</sub>, or R<sup>7</sup> and R<sup>8</sup> can be taken together with the N to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally contg., in addn. to the N, one or two addnl. heteroatoms = N, O and S; Ra = (C1-C6)alkyl, (C3-C6)cycloalkyl, aryl, or heterocyclyl; and Rb is H, (C1-C6)alkyl, aryl, heterocyclyl, (C3-C6)cycloalkyl, (C<sub>0</sub>)OC1-C6 alkyl, (C<sub>0</sub>)C1-C6 alkyl or S(O)<sub>2</sub>Ra. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC<sub>50</sub> values = 0.01-5.0 .mu.M. Although the methods of prepn. are not claimed, 3 example prepsn. are included.

IT 117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combined with indolylquinolinone tyrosine kinase inhibitors for treatments and/or prevention of various disorders)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

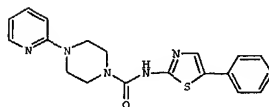
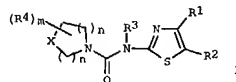


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 15 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:154246 CAPLUS  
 DOCUMENT NUMBER: 138:187764  
 TITLE: Preparation of 2-(azacycliccarbonylamino)thiazoles as tyrosine kinase inhibitors  
 INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.; Smith, Anthony M.; Lamma, William C., Jr.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 101 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015778	A1	20030227	WO 2002-US27156	20020813
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPL. INFO.:			US 2001-313234P P 20010817	
OTHER SOURCE(S):			MARPAT 138:187764	
GI				

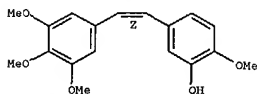


AB Title ureas I (wherein X = CH or NR<sup>3</sup>a; m = 1-6; n = independently 0-2; R<sup>1</sup> = H, halo, alkyl, or alkoxy; R<sup>2</sup> = (un)substituted aryl, CN, CONR<sup>a</sup>R<sup>b</sup>, halo, cycloalkyl, or C<sub>1</sub>trihydroxy; R<sup>3</sup> = H, alkyl, SO<sub>2</sub>Rd, CORd, or CO<sub>2</sub>Rd; R<sup>3</sup>a = per the definition of R<sup>3</sup> or substituted alkyl; R<sup>4</sup> = H, alkylene-NR<sup>5</sup>R<sup>6</sup>, CO<sub>2</sub>H, CO<sub>2</sub>Rd, halo, OH, alkoxy, or (un)substituted alkyl; R<sup>5</sup> and R<sup>6</sup> = independently H, alkyl, SO<sub>2</sub>Rd, CO<sub>2</sub>Rd, CORd, alkylene-NR<sup>a</sup>R<sup>b</sup>,

L24 ANSWER 15 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
alkylene-CONR<sub>a</sub>R<sub>b</sub>, or (un)substituted alkylene-heterocyclyl or aryl; or NR<sub>6</sub>R<sub>6</sub> = (un)substituted heterocyclyl; R<sub>a</sub> and R<sub>b</sub> = independently H, (cyclo)alkyl, Ph, CO<sub>2</sub>R<sub>d</sub>, COR<sub>d</sub>, or SO<sub>2</sub>R<sub>d</sub>; R<sub>c</sub> = H, Ph, or alkyl; R<sub>d</sub> = Ph or alkyl; or pharmaceutically acceptable salts or stereoisomers thereof) were prepd. for the inhibition, regulation, and/or modulation tyrosine kinase signal transduction. For example, reaction of 2-((4-nitrophenoxy)carbonyl)amino-5-phenylthiazole with 4-(2-pyridyl)piperazine in the presence of DIEA in DMF at 60.degree. for 1 h gave II. Tested I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC<sub>50</sub> values between 0.01 - 5.0 .mu.M. I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT 117048-59-6, Combretastatin A-4  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(combination therapy agent; prepn. of (azacycylcarbonylamino)thiazole tyrosine kinase inhibitors as angiogenesis inhibitors)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



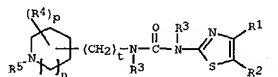
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2003:154204 CAPLUS  
DOCUMENT NUMBER: 138:165738  
TITLE: Tyrosine kinase inhibitors and their use in disease treatment  
INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.; Smith, Anthony M.; Lumma, William C., Jr.  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: PCT Int. Appl., 58 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015717	A2	20030227	WO 2002-US27149	20020813

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KS, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPL. INFO.: US 2001-313374P P 20010817  
OTHER SOURCE(S): MARPAT 138:165738  
GI

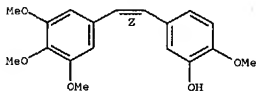


AB The present invention relates to compds. I (n = 1,2,3; p,t = 1,2; R<sub>1</sub> = H, halo, C1-8-alkyl; R<sub>2</sub> = Ph, CN, C1(0)NR<sub>a</sub>R<sub>b</sub>, halo, C3-6-cycloalkyl, C.tpbondCOR<sub>d</sub>; R<sub>3</sub> = H, halo, OH, C1-8-alkyl, C1-8-alkoxy; R<sub>5</sub> = H, Ph, C1-8-alkyl, CO<sub>2</sub>R<sub>d</sub>, C(0)R<sub>d</sub>, SO<sub>2</sub>R<sub>d</sub>; R<sub>a</sub>, R<sub>b</sub> = H, Ph, C1-8-alkyl, CO<sub>2</sub>R<sub>d</sub>, C(0)R<sub>d</sub>, SO<sub>2</sub>R<sub>d</sub>; R<sub>c</sub> = H, Ph, C1-8-alkyl; R<sub>d</sub> = Ph, C1-8-alkyl, benzyl) which inhibit, regulate and/or modulate tyrosine kinase signal transduction. I may be used to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. Thus, compds. such as N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea were prepd. and tested for effects on VEGF receptor kinase, FLT-1 kinase, and HUVEC mitogenesis. I compds. inhibited HUVEC mitogenesis with IC<sub>50</sub> values of 0.01-5.0 .mu.M.

IT 117048-59-6, Combretastatin A-4

L24 ANSWER 16 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(pharmaceuticals contg. tyrosine kinase inhibitors and tyrosine kinase inhibitors and their use in disease treatment)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

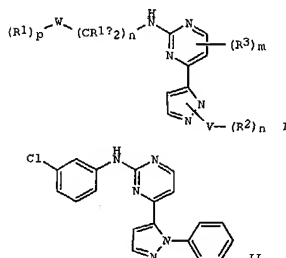


L24 ANSWER 17 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2003:117807 CAPLUS  
DOCUMENT NUMBER: 138:153548  
TITLE: Preparation of 4-(pyrazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors  
INVENTOR(S): Fraley, Mark E.; Peckham, Jennifer P.; Arrington, Kenneth L.; Hoffman, William F.; Hartman, George D.  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: PCT Int. Appl., 96 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011837	A1	20030213	WO 2002-US23879	20020726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KS, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

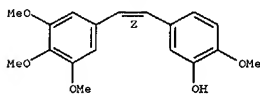
PRIORITY APPL. INFO.: US 2001-309399P P 20010801  
OTHER SOURCE(S): MARPAT 138:153548  
GI



AB The present invention relates to title compds. I [wherein R<sub>1a</sub> = H, (un)substituted alkyl, OR<sub>8</sub>, or N(R<sub>8</sub>)<sub>2</sub>; R<sub>1</sub> and R<sub>2</sub> = independently H, halo, CF<sub>3</sub>, (CH<sub>2</sub>)<sub>2</sub>tr9COR<sub>8</sub>, COR<sub>9</sub>, (CH<sub>2</sub>)<sub>2</sub>OR<sub>8</sub>, CN, (CH<sub>2</sub>)<sub>2</sub>NR<sub>7</sub>R<sub>8</sub>, (CH<sub>2</sub>)<sub>2</sub>CONR<sub>7</sub>R<sub>8</sub>, CO<sub>2</sub>R<sub>8</sub>,

L24 ANSWER 17 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 (CH<sub>2</sub>)tSOO-2(CH<sub>2</sub>)tNR7R8, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R<sub>3</sub> = independently H, CN, halo, N(R<sub>3</sub>)<sub>2</sub>, (CH<sub>2</sub>)tOR8, or (un)substituted (ar)alkyl or aryl; R<sub>7</sub> = independently H or (un)substituted (ar)alkyl; R<sub>8</sub> = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R<sub>9</sub> = independently (un)substituted heterocyclyl, alkyl, or aryl; V = a bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-2; n = 0-6; p = 0-4; t = independently 0-6; and pharmaceutically acceptable salts, hydrates, and stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-(methylthio)pyrimidine-4-carboxylic acid was amidated with dimethylhydroxylamine.bul.HCl in the presence of EDC and TEA, and the product treated with MeHgBr in Et<sub>2</sub>O to give 1-[2-(methylthio)pyrimidin-4-yl]ethanone. Coupling with N,N-dimethylformamide dimethylacetal followed by cyclization with phenylhydrazine afforded 2-(methylthio)-4-(1-phenyl-1H-pyrazol-3/5-yl)pyrimidine. Oxidn. with oxone and reaction with 3-chloroaniline provided the 4-(pyrazolyl)-2-pyrimidinamine II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC<sub>50</sub> values between 0.01 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).  
 IT 117048-59-6, Combretastatin A-4  
 RI: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (compn. components; prepn. of (pyrazolyl)pyrimidinamine tyrosine kinase inhibitors for treatment of angiogenesis, cancer, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



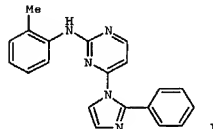
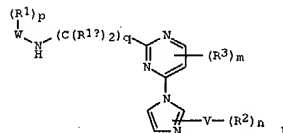
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:117806 CAPLUS  
 DOCUMENT NUMBER: 138:153547  
 TITLE: Preparation of 4-(imidazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors  
 INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Balitza, Adrienne; Rodman, Leonard; Hartman, George D.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 105 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011836	A1	20030213	WO 2002-US23764	20020726

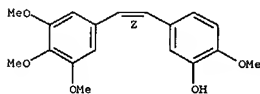
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-309400P P 20010801  
 OTHER SOURCE(S): MARPAT 138:153547  
 GI



L24 ANSWER 18 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, or OR8, or N(R8)2; R1 and R2 = independently H, halo, CF<sub>3</sub>, (CH<sub>2</sub>)tRSCOR8, COR8, (CH<sub>2</sub>)tOR8, CM, (CH<sub>2</sub>)tNR7R8, (CH<sub>2</sub>)tCOR8, CO2R8, (CH<sub>2</sub>)tSOq(CH<sub>2</sub>)tNR7R8, oxido, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R<sub>3</sub> = H, CN, halo, N(R<sub>3</sub>)<sub>2</sub>, (CH<sub>2</sub>)tOR8, or (un)substituted (ar)alkyl or aryl; R<sub>7</sub> = independently H or (un)substituted (ar)alkyl; R<sub>8</sub> = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R<sub>9</sub> = independently (un)substituted heterocyclyl, alkyl, or aryl; V = bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-3; n = 0-6; p = 0-4; q = undefined; t = 0-6; or pharmaceutically acceptable salts, hydrates or stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-phenylimidazole was coupled with 4-chloro-2-(methylthio)pyrimidine in the presence of NaH in DMF and the product oxidized using sodium tungstate dihydrate and H<sub>2</sub>O<sub>2</sub> in EtOAc to give 2-(methylsulfonyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine. Substitution with 2-methylaniline and purifn. by reverse phase chromatog. afforded II.bul.TFA. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC<sub>50</sub> values between 0.01 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).  
 IT 117048-59-6, Combretastatin A-4  
 RI: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (prepn. of (imidazolyl)pyrimidinamines as tyrosine kinase inhibitors)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



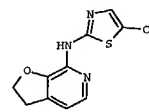
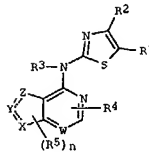
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:97306 CAPLUS  
 DOCUMENT NUMBER: 138:137303  
 TITLE: Preparation of fused heterocycle substituted aminothiazolecarbonitriles as tyrosine kinase inhibitors  
 INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Hartman, George D.  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 84 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003009852	A1	20030206	WO 2002-US23191	20020719

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-307443P P 20010724  
 OTHER SOURCE(S): MARPAT 138:137303  
 GI

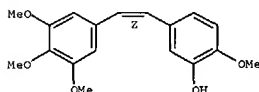


AB The present invention relates to the prepn. of title compds. I [wherein X, Y, and Z = C, S, N, or O, provided that at least one of X, Y, or Z = C; W = C or N; n = 0-6; R1, R2, and R4 = independently H, perfluoroalkyl(oxyl), OH, CN, halo, or (un)substituted (CO)rOs-alkyl, (CO)rOs-alkenyl, (CO)rOs-alkynyl, (CO)rOs-aryl, (CO)rOs-heterocyclyl, or alkyl-NR8Rb; R<sub>3</sub> = H, SO<sub>2</sub>Rc, (CO)rRc, or CO<sub>2</sub>Rc; R<sub>5</sub> = R<sub>3</sub> or Or(CO)nNR8Rb, halo, OH, oxo, perfluoroalkyl(oxyl), CHO, CO<sub>2</sub>H, CN, or (un)substituted (CO)rOs-aryl, (CO)rOs-heterocyclyl, or (CO)rOs-alkyl; r = 0-1; s = 0-1; Ra and Rb = independently H, SO<sub>2</sub>Rc, CO<sub>2</sub>Rc, or (un)substituted (CO)r-alkyl, (CO)r-heterocyclyl, or (CO)r-aryl; or NR8Rb = (un)substituted monocyclic or bicyclic heterocycle; Rc = (un)substituted alkyl, aryl, benzyl, or

L24 ANSWER 19 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 heterocyclyl; or pharmaceutically acceptable salts or stereoisomers thereof], which inhibit, regulate, and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 7-bromofuro[2,3-c]pyridine was converted to the amine using benzophenone imine, NaOBu-t, racemic BINAP, and Pd2(dba)3 in dry toluene and then hydrogenated with 10% Pd/C in AcOH to give 2,3-dihydrofuro[2,3-c]pyridin-7-amine. Addn. of 2-chloro-5-cyanothiazole in the presence of NaH in THF afforded the (furo[2,3-c]pyridin-7-yl)thiazolecarboxamide II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT 117048-59-6, Combretastatin A4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (compn. component; prepn. of fused heterocycle substituted aminothiazolecarboxamides as tyrosine kinase inhibitors)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:57889 CAPLUS  
 DOCUMENT NUMBER: 138:112414  
 TITLE: Compositions and methods of administering tubulin-binding agents for the treatment of ocular diseases  
 INVENTOR(S): Sherria, David; Wood, Mark  
 PATENT ASSIGNEE(S): Oxigene, Inc., USA  
 SOURCE: PCT Int. Appl., 59 pp.  
 CODEN: PFXKD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006002	A1	20030123	WO 2002-US22449	20020715

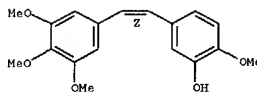
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PRIORITY APPLN. INFO.: US 2002-377556P P 20020502  
 US 2002-377845P P 20020503

AB The present invention is directed to the administration of vascular targeting agents, particularly a tubulin-binding agent, for the treatment of ocular neovascularization, ocular tumors, and conditions such as diabetic retinopathy, retinopathy of prematurity, retinoblastoma and macular degeneration.

IT 117048-59-6, Combretastatin A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

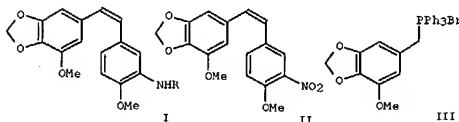
Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 20 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2003:20798 CAPLUS  
 DOCUMENT NUMBER: 138:221804  
 TITLE: Antineoplastic Agents. 487. Synthesis and Biological Evaluation of the Antineoplastic Agent 3,4-Methylenedioxy-5,4'-dimethoxy-3'-amino-Z-stilbene and Derived Amino Acid Amides  
 AUTHOR(S): Pettit, George R.; Anderson, Collin R.; Herald, Delbert L.; Jung, M. Katherine; Lee, Debbie J.; Hamel, Ernest; Pettit, Robin K.  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Journal of Medicinal Chemistry (2003), 46(4), 525-531  
 CODEN: JMCNAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI

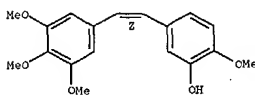


AB An efficient synthesis of 3,4-methylenedioxy-5,4'-dimethoxy-3'-amino-Z-stilbene, I (R = H), and its hydrochloride salt is reported. Nitrostilbene II was obtained via a Wittig reaction using phosphonium bromide III and 3-nitro-4-methoxybenzaldehyde. A one-step redn. of II using zinc in acetic acid produced I (R = H). The coupling of I (R = H) with various Fmoc amino acids (Cys, Gly, Phe, Ser, Trp, Tyr, Val), followed by cleavage of the .alpha.-amino protecting group, resulted in a series of new cancer cell growth inhibitory amides. I (R = H), its HCl salt, glycine amide I (R = COCH2NH2), and tyrosine amide I [R = COCH(CH2CH(OH)4)NH2] had the highest level (GI50 = 10-2-10-3 .mu.g/mL) of activity against a panel of six human and one animal (P388) cancer cell lines. I (R = H) and its hydrochloride salt potentially inhibited tubulin polymerization by binding at the colchicine site, while the amino acid amides had little activity against purified tubulin. Nevertheless, most of the amides caused a marked increase in the mitotic index of treated cells, indicating that tubulin was their intracellular target.

IT 117048-59-6, Combretastatin A4  
 RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (prepn. and biol. evaluation of amino acid amides of Z-stilbene derivs. as antineoplastic and antimicrobial agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 21 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

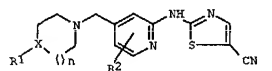


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:5956 CAPLUS  
DOCUMENT NUMBER: 138:73254  
TITLE: Preparation of thiazolylaminopyridines as tyrosine kinase inhibitors with therapeutic uses  
INVENTOR(S): Bilodeau, Mark T.; Hartman, George D.  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: PCT Int. Appl., 93 pp.  
CODEN: PINXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000687	A1	20030103	WO 2002-US21110	20020618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NZ, NO, NZ, OH, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TH, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ZY, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG US 2003100567 A1 20030529 US 2002-174774 20020619 PRIORITY APPL. INFO.: US 2001-300245P P 20010622 OTHER SOURCE(S): MARPAT 138:73254 G1				

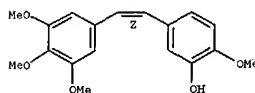


AB The present invention relates to thiazolylaminopyridines (shown as I; variables defined below; e.g. 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. For I: n is 0 or 1; X is C-H or N, provided X is C-H if n = 1 and R1 is SO2-(Cl-C6 alkyl) and provided that X is C-H if R1 is NH(C10)NR3H; R1 is SO2-(Cl-C6 alkyl), (C10)NR3H, or NH(C10)NR3H; R2 is H, OH, OCl-C6 alkyl, Cl-C6 alkyl, or halo; and R3 is Cl-C6 alkyl. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values = 0.01-5.0 .mu.M. 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide, 2-[[4-[(methylsulfonyl)piperidin-1-yl]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile, and 4-[2-(5-cyanothiazol-2-ylamino)-3-methylpyridin-4-

L24 ANSWER 22 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
ylmethyl]piperazine-1-carboxylic acid methylamide show enhanced pharmacokinetic properties as compared to previously reported thiazolylaminopyridines in WO 01/17995 A1. Although the methods of prepn. are not claimed, 13 example prepn. are included.

IT 117048-59-6, Combrexastatin A-4  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (in combination with thiazolylaminopyridine tyrosine kinase inhibitors for various therapies)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

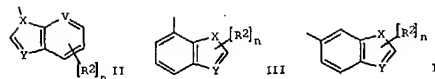
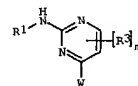


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 23 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:977797 CAPLUS  
DOCUMENT NUMBER: 138:55974  
TITLE: Preparation of 2-anilino-4-(indol-1-yl)pyrimidines as tyrosine kinase inhibitors  
INVENTOR(S): Kim, Yuntae; Hanney, Barbara  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
SOURCE: PCT Int. Appl., 82 pp.  
CODEN: PINXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

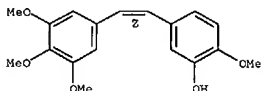
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102783	A1	20021227	WO 2002-US18907	20020614
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NZ, NO, NZ, OH, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TH, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ZY, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG PRIORITY APPL. INFO.: US 2001-299343P P 20010619 OTHER SOURCE(S): MARPAT 138:55974 G1				



AB The title compds. (I; W = II-IV; X, Y = C, N, provided that when X = N, then Y = C and when X = C, then Y = N; V = C, N; R1 = (un)substituted aryl, heterocyclyl; R2 = H, halo, alkyl, etc.; R3 = H, alkyl, aryl, etc.; m = 0-2; n = 0-5) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, and therefore are useful in treating tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were prepd. E.g., a multi-step synthesis of I (W = 4-fluoro-1H-indol-1-yl; R1 = Ph; R3 = H), starting from 2-thiouracil, was given.

L24 ANSWER 23 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 IT 117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (prepn. of 2-anilino-4-(indol-1-yl)pyrimidines as tyrosine kinase  
 inhibitors and their use in combination with)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 24 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:942701 CAPLUS  
 DOCUMENT NUMBER: 138:8413  
 TITLE: Vascular implants treated with FK506  
 INVENTOR(S): Wendt, Stephan; Von Oepen, Randolph; Kuttler, Bernd;  
 Lang, Gerhard  
 PATENT ASSIGNEE(S): Jomed G.m.b.H., Germany  
 SOURCE: Ger. Offen., 22 pp.  
 CODEN: GWXXRX  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10127330	A1	20021212	DE 2001-10127330	20010606

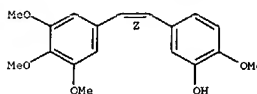
PRIORITY APPLN. INFO.: DE 2001-10127330 20010606

AB The invention concerns vascular implants that include a metal, or an alloy base, a ceramic or polymer coating and covalently bound or phys. immobilized FK506 for the treatment of stenosis and restenosis. In addn., the implants can include other drugs. For the prepn., the coated implant is incubated with a soln. of FK506; or FK506 is added during polymn. coating.

IT 117048-59-6, Combretastatin A4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (vascular implants treated with FK506)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 25 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:941572 CAPLUS  
 DOCUMENT NUMBER: 138:8411  
 TITLE: Vascular implants treated with FK506  
 INVENTOR(S): Wendt, Stephan; Von Oepen, Randolph; Kuttler, Bernd;  
 Lang, Gerhard  
 PATENT ASSIGNEE(S): Jomed G.m.b.H., Germany  
 SOURCE: Ger. Offen., 22 pp.  
 CODEN: GWXXRX  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10127011	A1	20021212	DE 2001-10127011	20010605

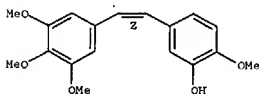
PRIORITY APPLN. INFO.: DE 2001-10127011 20010605

AB The invention concerns vascular implants that include a metal, or an alloy base, a ceramic or polymer coating and covalently bound or phys. immobilized FK506 for the treatment of stenosis and restenosis. In addn., the implants can include other drugs. For the prepn., the coated implant is incubated with a soln. of FK506; or FK506 is added during polymn. coating.

IT 117048-59-6, Combretastatin A4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (vascular implants treated with FK506)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

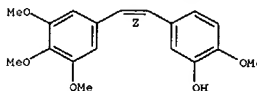
L24 ANSWER 26 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:925011 CAPLUS  
 TITLE: Structure-activity and crystallographic analysis of  
 benzophenone derivatives-the potential anticancer  
 agents  
 AUTHOR(S): Hsieh, Hsing-Fang; Liou, Jing-Fang; Lin, Ying-Ting;  
 Mahindroo, Neeraj; Chang, Jang-Yang; Yang, Yung-Ning;  
 Chern, Shuen-Shing; Tan, Uan-Kang; Chang, Chun-Wei;  
 Chen, Tung-Wei; Lin, Chi-Hung; Chang, Ying-Ying; Wang,  
 Chiung-Chiu  
 CORPORATE SOURCE: Sec. 6, Division of Biotechnology and Pharmaceutical  
 Research, National Health Research Institutes, Taipei,  
 Taiwan, 114, Peop. Rep. China  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2003),  
 13(1), 101-105  
 CODEN: BMCLEB; ISSN: 0960-894X  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Compd. 1-5, structurally related to combretastatin A-4 showed excellent cytotoxic activities against a panel of human cancer cell lines including multi-drug resistant cell lines. The x-ray three-dimensional structural anal. shows that proton donor in B ring may be required for cytotoxic activity, with intermol. hydrogen bonding playing an important role.

IT INDEXING IN PROGRESS  
 IT 117048-59-6, Combretastatin A-4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (structure-activity and crystallog. anal. of benzophenone deriva. as potential antitumor agents)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 27 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:793477 CAPLUS  
 DOCUMENT NUMBER: 137:293582  
 TITLE: Anti-CD19 immunotoxins and their use in immunotherapy  
 INVENTOR(S): Olson, William C.; Maddon, Paul J.; Ma, Dangshe  
 PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 46 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080987	A1	20021017	WO 2002-US9889	20020329
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AA, AZ, BY, KG, KZ, MD, RU, TJ, TM, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

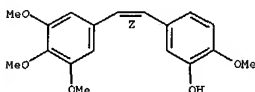
PRIORITY APPL. INFO.: US 2001-282587 P 20010409

AB The invention relates to therapeutic methods using compns. including immunotoxins based on antibodies that specifically bind the B cell membrane protein CD19. Anti-CD19 immunotoxins, compns. contg. such immunotoxins, and methods for using the immunotoxins are provided. The immunotoxins can be labeled with radionuclides, chemotherapeutic agents, or immunomodulators. The immunotoxins can be used in the treatment of B-cell malignancies, various autoimmune diseases, and organ/tissue transplants.

IT 117048-59-6D, Combretastatin A4, immunotoxin labeled  
 RL: RSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anti-CD19 immunotoxins for treatment of B-cell malignancy, autoimmune diseases, and transplants)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 28 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:736049 CAPLUS  
 DOCUMENT NUMBER: 137:253007  
 TITLE: A combination comprising combretastatin and anticancer agents  
 INVENTOR(S): Blumery, Maria-Christine  
 PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.  
 SOURCE: PCT Int. Appl., 19 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074229	A2	20020926	WO 2002-BF3322	20020315
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AA, AZ, BY, KG, KZ, MD, RU, TJ, TM, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

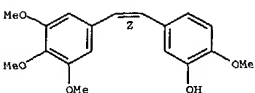
PRIORITY APPL. INFO.: US 2002-92508 20020308  
 US 2003060429 A1 20030327 US 2002-97926 20020315  
 US 2001-275627 P 20010315

AB An antitumor combination comprising a stilbene deriv. and an anticancer compd. selected from the group consisting of taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics as the active ingredients is provided. Methods of using these pharmaceutical preps. for the treatment of solid carcinomas are also provided. Thus, an infusion formulation contained combretastatin 2 hydrochloride 5 mg, Tween-80 0.5 mL and saline soln. 9.5 mL. The combination of combretastatin 2 and cisplatin synergistic.

IT 117048-59-6, Combretastatin A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combination comprising combretastatin and anticancer agents)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 27 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 29 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:682260 CAPLUS  
 DOCUMENT NUMBER: 138:226477  
 TITLE: Combretastatin-A4 prodrug induces mitotic catastrophe in chronic lymphocytic leukemia cell line independent of caspase activation and poly(ADP-ribose) polymerase cleavage  
 AUTHOR(S): Nabha, Sanaa M.; Mohammad, Ramzi M.; Dandashi, Mahmoud K.; Coupaye-Gerard, Brigitt; Aboukamel, Amro; Pettit, George R.; Al-Katib, Ayad M.  
 CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA  
 SOURCE: Clinical Cancer Research (2002), 8(8), 2735-2741  
 CODEN: CCREF4; ISSN: 1078-0432  
 PUBLISHER: American Association for Cancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The authors have previously reported that combretastatin-A4 prodrug (CAAP), an antitubulin/antiangiogenic agent isolated from the South African willow tree Combretum caffrum, induced cell death primarily through mitotic catastrophe in a panel of human B-lymphoid tumors. In this study, the authors investigated the mol. aspects of the mitotic catastrophe and whether or not it shares the same pathways of apoptosis. For this the authors studied the effect of CAAP on selected markers of apoptosis (caspases 9 and 3, poly(ADP-ribose) polymerase (PARP), bcl-2, and bax) and G2-M protein regulators (p53, MDM2, 14-3-3, vsmg, GADD45, cdc2, cdc25, chk1, weel, p21, and cyclin B1). The chronic lymphocytic leukemia cell line WSU-CLL was used for this purpose. Western blot anal. showed that 24 h of CAAP (5 nM) exposure induces caspase 9 activation and PARP cleavage. However, the addn. of Z-Val-Ala-Asp-fluoromethylketone (a general caspase inhibitor) or Z-Leu-Glu(OMe)-His-Asp(OMe)-CH2F (a caspase 9 inhibitor) before CAAP treatment did not block cell death. No change in bcl-2 or bax protein expression was obsd. Exposure of WSU-CLL cells to 4 and 5 nM CAAP was assocd. with overprod. of total p53 and no dramatic change in MDM2, 14-3-3, vsmg, GADD45, the cyclin-dependent kinase cdc2, its inhibitory phosphorylation, the cdc2-inhibitory kinase (weel), chk1, or cdc25 hyperphosphorylation. The overaccumulation of p21 and cyclin B1 protein was obvious at 24 h. Furthermore, CAAP treatment showed an increase in the expression of a marker of mitosis (mitotic protein monoclonal-2 antibody) and an overaccumulation of the cyclin B in the nucleus. The authors' findings suggest that CAAP induces mitotic catastrophe and arrest of WSU-CLL cells mostly in the M phase independent of p53 and independent of chk1 and cdc2 phosphorylation pathways. Apoptosis is a 2ndary mechanism of death in a small proportion of cells through activation of caspase 9 and PARP cleavage. The 2 mechanisms of cell death, i.e., mitotic catastrophe and apoptosis, are independent of each other in the authors' model.

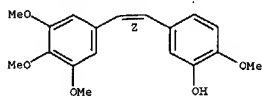
IT 117048-59-6P, Combretastatin-A4  
 RL: DWA (Drug mechanism of action); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (combretastatin-A4 action mechanism in chronic lymphocytic leukemia cells)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 29 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 30 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:621729 CAPLUS  
DOCUMENT NUMBER: 138:147033  
TITLE: The biology of the combretastatins as tumour vascular targeting agents

AUTHOR(S): Tozer, Gillian M.; Kanthou, Chrysos; Parkins, Charles S.; Hill, Sally A.  
CORPORATE SOURCE: Gray Cancer Institute, Middlesex, UK  
SOURCE: International Journal of Experimental Pathology (2002), 83(1), 21-38  
CODEN: IJEPD; ISSN: 0959-9673

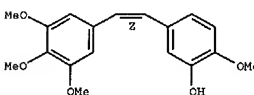
PUBLISHER: Blackwell Science Ltd.  
DOCUMENT TYPE: Journal: General Review  
LANGUAGE: English

AB A review. The tumor vasculature is an attractive target for therapy. Combretastatin A-4 (CA-4) and A-1 (CA-1) are tubulin binding agents, structurally related to colchicine, which induce vascular-mediated tumor necrosis in animal models. CA-1 and CA-4 were isolated from the African bush willow, Combretum caffrum, and several synthetic analogs are also now available, such as the Aventis Pharma compd., AVE8062. More sol., phosphorylated, forms of CA-4 (CA-4-P) and CA-1 (CA-1-P) are commonly used for in vitro and in vivo studies. These are cleaved to the natural forms by endogenous phosphatases and are taken up into cells. The lead compd., CA-4-P, is currently in clin. trial as a tumor vascular targeting agent. In animal models, CA-4-P causes a prolonged and extensive shutdown of blood flow in established tumor blood vessels, with much less effect in normal tissues. This paper reviews the current understanding of the mechanism of action of the combretastatins and their therapeutic potential.

IT 117048-59-6, Combretastatin A-4  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(biol. of combretastatins as tumor vascular targeting agents)

RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 31 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:555278 CAPLUS  
DOCUMENT NUMBER: 137:119643  
TITLE: Methods using a combretastatin compound combined with an antitumor agent for modulating tumor growth and metastasis

INVENTOR(S): Lee, Francis Y.; Peck, Ronald; Chaplin, David; Pero, Ronald; Edwardsen, Klaus  
PATENT ASSIGNER(S): Bristol-Myers Squibb Company, USA; Oligene, Inc.  
SOURCE: PCT Int. Appl., 69 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

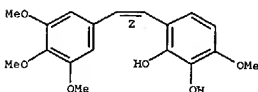
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002056692	A1	20020725	WO 2001-US50261	20011220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GR, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LI, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, HL, HR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2000-258195P F 20001222  
AB Methods and pharmaceutical compns. for modulating tumor growth or metastasis are provided. The methods of the invention use combinations of a combretastatin compd. and an antitumor agent.

IT 109971-63-3, Combretastatin A1 109971-63-3D,  
Combretastatin A1, derivs. 117048-59-6, Combretastatin A4  
117048-59-6D, Combretastatin A4, derivs.  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(combretastatin compd. combined with antitumor agent for modulating tumor growth and metastasis)

RN 109971-63-3 CAPLUS  
CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

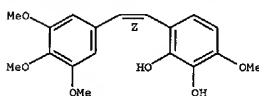
Double bond geometry as shown.



RN 109971-63-3 CAPLUS  
CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

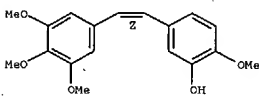
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L24 ANSWER 31 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



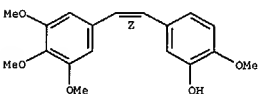
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 32 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:521462 CAPLUS  
 DOCUMENT NUMBER: 137:88442  
 TITLE: Incensole and furanogermacrenes and compounds in treatment for inhibiting neoplastic lesions and microorganisms

INVENTOR(S): Shanahan-Pendergast, Elisabeth  
 PATENT ASSIGNEE(S): Ire.  
 SOURCE: PCT Int. Appl., 68 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

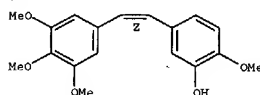
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-1E1	20020102
WO 2002053138	A3	20020919		
W: AE, AG, AT, AU, BE, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: IR 2001-2 A 20010102

OTHER SOURCE(S): MARPAT 137:88442  
 AB The invention discloses the use of incensole and/or furanogermacrenes, derive, metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immunoregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacrenes and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

IT 117048-59-6, Combretastatin A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical formulation further including: incensole and furanogermacrenes and compds. as antitumor and antimicrobial agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:487508 CAPLUS  
 DOCUMENT NUMBER: 137:47052  
 TITLE: Preparation of substituted stilbenes as antitumor agents

INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John  
 PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK  
 SOURCE: PCT Int. Appl., 76 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		

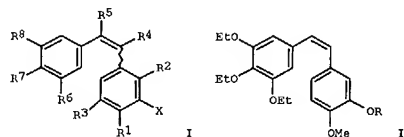
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002016228 A5 20020701 AU 2002-16228 20011220  
 PRIORITY APPLN. INFO.: GB 2000-31262 A 20001221  
 GB 2001-295 A 20010105  
 WO 2001-GB5702 W 20011220

OTHER SOURCE(S): MARPAT 137:47052

GI



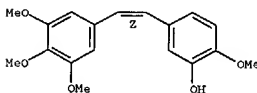
AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3,

L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR, R6, R7, R8 = H, alkyl, alkoxy; zigzag bond = cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butylidimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.

IT 117048-59-6, Combretastatin A-4  
 RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (prepn. of substituted stilbenes as antitumor agents)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

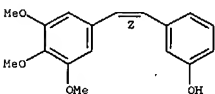
Double bond geometry as shown.



IT 160422-43-5P 438534-24-8P 438534-68-0P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of substituted stilbenes as antitumor agents)

RN 160422-43-5 CAPLUS  
 CN Phenol, 3-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

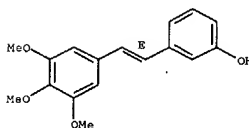
Double bond geometry as shown.



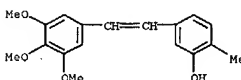
RN 438534-24-8 CAPLUS  
 CN Phenol, 3-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



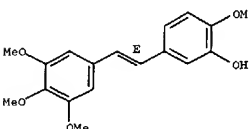
RN 438534-68-0 CAPLUS  
 CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



IT 117048-62-1  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (prepn. of substituted stilbenes as antitumor agents)

RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

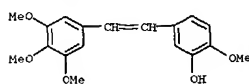
Double bond geometry as shown.



IT 438534-81-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. of substituted stilbenes as antitumor agents)

RN 438534-81-7 CAPLUS  
 CN Phenol, 2-methoxy-5-[(2-(3,4,5-trimethoxyphenyl)ethenyl)- (9CI) (CA INDEX NAME)

L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

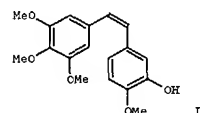
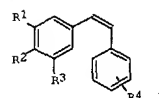


L24 ANSWER 34 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:487498 CAPLUS  
 DOCUMENT NUMBER: 137:47051  
 TITLE: Materials and methods for synthesizing stilbenes  
 INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Gukroger, Keira; Hepworth, Lucy Annette; Lawrence, Nicholas James  
 PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK  
 SOURCE: PCT Int. Appl., 38 pp.  
 CODEN: FIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002049994	A2	20020627	WO 2001-GB5534	20011214
WO 2002049994	A3	20021017		

W: AB, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LI, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, YG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, DE, BJ, CF, CG, CI, CM, GA, GG, GW, ML, MR, NE, SN, TD, TG  
 AU 2002017267 A5 20020701 AU 2002-17267 20011214  
 PRIORITY APPL. INFO.: GB 2000-31263 A 20001221  
 WO 2001-GB5534 W 20011214  
 OTHER SOURCE(S): CASREACT 137:47051; MARPAT 137:47051  
 GI

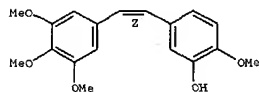


AB The present invention relates materials and methods for synthesizing stilbenes of formula I (R1-R3 = H, OH, NO2, NH2, aryl, heteroaryl, alkyl, alkoxy, halo, etc.; R4 = H, OH, NO2, NH2, alkyl, alkoxy, etc. (one, two or three substituents)), and in particular to processes for the synthesis of substituted stilbenes such as combretastatin A4 (II). The present invention relates in particular to methods which are stereoselective for either the cis or the trans isomer of the substituted stilbene, using a Perkin-type condensation of an arylacetic acid and a substituted benzaldehyde, followed by a decarboxylation reaction to produce the substituted cis-stilbenes or a Suzuki-type reaction involving a Z or

L24 ANSWER 34 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

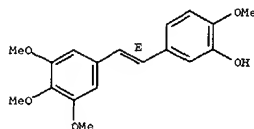
E-ethenyl halide and a substituted boronic acid in the presence of a palladium catalyst to produce specifically either the Z or E-isomer of substituted stilbenes. Thus, 3-hydroxy-4-methoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid were reacted in acetic anhydride with triethylamine, then the product was decarboxylated with copper in quinoline to give II.  
 IT 117048-59-6P, Combretastatin A4  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of combretastatin A4)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 117048-62-1P, trans-Combretastatin A4  
 RL: SYN (Synthetic preparation); PREP (Preparation)  
 (synthesis of combretastatin A4)  
 RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 35 OF 157 CAPLUS COPYRIGHT 2003 ACS

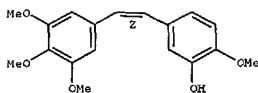
ACCESSION NUMBER: 2002:471932 CAPLUS  
 DOCUMENT NUMBER: 137:163285  
 TITLE: A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin A-4 phosphate on a single-dose intravenous schedule in patients with advanced cancer  
 AUTHOR(S): Dowlati, Afshin; Robertson, Kelly; Cooney, Matthew; Petros, William P.; Stratford, Michael; Jesberger, John; Rafie, Niusah; Overmeyer, Beth; Makkar, Vinit; Stambler, Bruce; Taylor, Anne; Voss, John; Lewin, Jonathan S.; McCrae, Keith R.; Remick, Scott C.  
 CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, School of Medicine, Case Western Reserve University (CWRU), Cleveland, OH, 44106, USA  
 SOURCE: Cancer Research (2002), 62(12), 3408-3416  
 CODEN: CNREAH; ISSN: 0008-5472  
 PUBLISHER: American Association for Cancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Combretastatin A-4 phosphate (CA4P) is a novel antitumor vascular targeting agent, the first agent of this class of compds. to enter the clinic. We performed a Phase I trial to det. the max.-tolerated dose, safety, and pharmacokinetic profile of CA4P on a single-dose i.v. schedule. We also obtained preliminary data on its effect on tumor blood flow using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques and cell adhesion mols. at the higher-dose levels. Twenty-five assessable patients with advanced cancer received a total of 107 cycles over the following dose escalation schema: 18, 36, 60, 90 mg/m2 as a 10-min infusion and 60 mg/m2 as a 60-min infusion at 3-wk intervals. There was no significant myelotoxicity, stomatitis, or alopecia. Tumor pain was a unique side effect, which occurred in 10% of cycles, and there were four episodes of dose-limiting toxicity at dosages .gtoreq.60 mg/m2, including two episodes of acute coronary syndrome. Pharmacokinetics revealed rapid dephosphorylation of the parent compd. (CA4P) to combretastatin A4 (CA4), with a short plasma half-life (.apprx.30 min). A significant (P < 0.03) decline in gradient peak tumor blood flow by DCE-MRI in six of seven patients treated at 60 mg/m2 was obsd. A patient with anaplastic thyroid cancer had a complete response and is alive 30 mo after treatment. The toxicity profile is consistent with a drug that is "vascularly active" and devoid of traditional "cytotoxic" side effects. Dosages .gtoreq.60 mg/m2 as a 10-min infusion define the upper boundary of the max.-tolerated dose.

IT 117048-59-6, Combretastatin A4  
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BICL (Biological study); USES (Uses)  
 (pharmacokinetic and translational study of novel vascular targeting agent combretastatin A-4 phosphate on a single-dose i.v. schedule in patients with advanced cancer)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 35 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 36 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:449449 CAPLUS

DOCUMENT NUMBER: 137:33318

TITLE:

Preparation of pyrimidinylaminothiazoles as tyrosine kinase inhibitors.

INVENTOR(S):

Bilodeau, Mark T.; Hartman, George D.; Hoffman, Jacob M., Jr.; Lumma, William C., Jr.; Manley, Peter J.; Rodman, Leonard; Sisko, John T.; Smith, Anthony M.; Tucker, Thomas J.

PATENT ASSIGNEE(S):

Merck &amp; Co., Inc., USA

SOURCE:

PCT Int. Appl., 169 pp.

DOCUMENT TYPE:

CODEN: PXX02

LANGUAGE:

Patent

FAMILY ACC. NUM. COUNT: 1

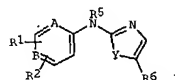
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002045652	A2	20020613	WO 2001-US44573	20011130
WO 2002045652	A3	20020822		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KR, KS, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002137755	A1	20020926	US 2001-990473	20011121
AU 2002032441	A5	20020618	AU 2002-32441	20011130
PRIORITY APPLN. INFO.:			US 2000-251006P	P 20001204
			WO 2001-US44573	W 20011130

OTHER SOURCE(S):

MARPAT 137:33318

GI



AB Title compds. [I; A, B = N, NO; Y = O, S, NR4; R1, R2 = H, perfluoroalkoxy, OH, cyano, halo, (substituted) alkyl(oxy)(carbonyl), aryl(oxy)(carbonyl), heterocyclyl, etc.; R4 = H, aryl, alkyl; R5 = H, SO2R6, COR6, R6 = aryl, cyano, halo, (substituted) alkyl, alkynyl, alkynyl, heterocyclyl, aminocarbonyl; R6 = alkyl, aryl, heterocyclyl], were prepd. for treating angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammation, etc. Thus, 4-aminopyrimidine was stirred with NaH in THF; 2-bromo-5-phenylthiazole was added and the mixt. was refluxed overnight to give 5-phenylthiazol-2-yl pyrimidin-4-yl amine. I inhibited

L24 ANSWER 36 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

vascular endothelial growth factor-stimulated mitogenesis of human vascular endothelial cells with IC50 = 0.01-5.0 nM.

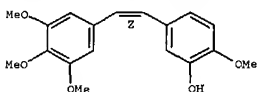
IT

117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (coadministration; prepn. of pyrimidinylaminothiazoles as tyrosine kinase inhibitors)

RN

117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 37 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:348358 CAPLUS

DOCUMENT NUMBER: 137:87838

TITLE:

Antineoplastic Agents. 465. Structural Modification of Resveratrol: Sodium Resverastatin Phosphate

AUTHOR(S):

Pettit, George R.; Grealish, Matthew P.; Jung, M. Katherine; Hamel, Ernest; Pettit, Robin K.; Chapuis, J. Charles; Schmidt, Jean M.

CORPORATE SOURCE:

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA

SOURCE:

Journal of Medicinal Chemistry (2002), 45(12), 2534-2542

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER:

American Chemical Society

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 137:87838

AB

As an extension of structure/activity investigations of resveratrol, phenstatin, and the cancer antiangiogenesis drug sodium combretastatin A-4 phosphate, syntheses of certain related stilbenes and benzophenones were undertaken. The tri-Me ether deriv. of (Z)-resveratrol exhibited the strongest activity (GI50 = 0.01-0.001 μM/g/mL) against a minipanel of human cancer cell lines. A monodemethylated deriv. was converted to prodrug (sodium resverastatin phosphate) for further biol. evaluation. The antitubulin and antimicrobial activities of selected compds. were also evaluated.

IT

117048-59-6, Combretastatin A-4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

RN

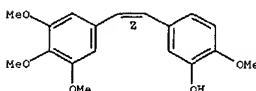
117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

CN

Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

INDEX NAME)

Double bond geometry as shown.



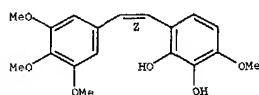
REFERENCE COUNT:

48

THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 38 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:255740 CAPLUS  
 DOCUMENT NUMBER: 137:140374  
 TITLE: Direct biocoxidation of arenes to corresponding catechols with *E. coli* JM109 (pDTG602). Application to synthesis of combretastatins A-1 and B-1  
 AUTHOR(S): Rui, Yu P.; Hudlicky, Tomas; Hansen, Trond V.; Stenstrom, Yngve  
 CORPORATE SOURCE: Department of Chemistry, University of Florida, Gainesville, FL, 32611-7200, USA  
 SOURCE: Tetrahedron Letters (2002), 43(15), 2839-2841  
 CODEN: TELRAY; ISSN: 0040-4039  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 137:140374  
 AB Convergent syntheses of combretastatins A-1 and B-1 were accomplished via coupling of biocatalytically generated p-bromomethoxycatechol with trimethoxyphenylacetylene.  
 IT 109971-63-3P, Combretastatin A-1  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of combretastatins A-1 and B-1 via biocidn. with *E. coli* JM109 and coupling of bromomethoxycatechol with (trimethoxyphenyl)acetylene)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



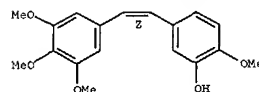
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 39 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:243561 CAPLUS  
 DOCUMENT NUMBER: 137:242112  
 TITLE: Inhibition of proliferative retinopathy by the anti-vascular agent combretastatin-A4  
 AUTHOR(S): Griggs, Jeremy; Skepper, Jeremy N.; Smith, Garry A.; Brindle, Kevin M.; Metcalfe, James C.; Hesketh, Robin  
 CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK  
 SOURCE: American Journal of Pathology (2002), 160(3), 1097-1103  
 CODEN: AJPA44; ISSN: 0002-9440  
 PUBLISHER: American Society for Investigative Pathology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Retinal neovascularization occurs in a variety of diseases including diabetic retinopathy, the most common cause of blindness in the developed world. There is accordingly considerable incentive to develop drugs that target the aberrant angiogenesis assoc. with these conditions. Previous studies have shown that a no. of anti-angiogenic agents can inhibit retinal neovascularization in a well-characterized murine model of ischemia-induced proliferative retinopathy. Combretastatin-A4 (CA-4) is an anti-vascular tubulin-binding agent currently undergoing clin. evaluation for the treatment of solid tumors. We have recently shown that CA-4 is not tumor-specific but elicits anti-vascular effects in nonneoplastic angiogenic vessels. In this study we have examd. the capacity of CA-4 to inhibit retinal neovascularization in vivo. CA-4 caused a dose-dependent inhibition of neovascularization with no apparent side effects. The absence of vascular abnormalities or remnants of disrupted neovessels in retinas of CA-4-treated mice suggests an anti-angiogenic mechanism in this model, in contrast to the anti-vascular effects obsd. against established tumor vessels. Importantly, histol. and immunohistochem. analyses indicated that CA-4 permitted the development of normal retinal vasculature while inhibiting aberrant neovascularization. These data are consistent with CA-4 eliciting tissue-dependent anti-angiogenic effects and suggest that CA-4 has potential in the treatment of nonneoplastic diseases with an angiogenic component.

IT 117048-59-6, Combretastatin-A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (inhibition of proliferative retinopathy by combretastatin-A4)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 39 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

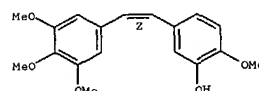
L24 ANSWER 40 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:220602 CAPLUS  
 DOCUMENT NUMBER: 136:268115  
 TITLE: Combretastatin A-4 phosphate prodrug mono- and di-organic amine salts, mono- and di- amino acid salts, and mono- and di-amino acid ester salts  
 INVENTOR(S): Venit, John J.; Dali, Mandar V.; Dali, Manisha M.; Huang, Yande; Dahlheim, Charles E.; Tejwani, Ravindra W.  
 PATENT ASSIGNER(S): Bristol-Myers Squibb Company, USA  
 SOURCE: PCI Int. Appl., 84 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002022626	A1	20020321	WO 2001-US28401	20010912
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, FI, GB, GD, GE, GH, GI, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GN, GG, GW, HT, HR, NE, SN, TD, TG			
US 2002072507	A1	20020613	US 2001-950500	20010911
AU 2001090771	A5	20020326	AU 2001-90771	20010912
BR 2001007210	A	20030225	BR 2001-7210	20010912
NO 200202270	A	20020701	NO 2002-2270	20020513
PRIORITY APPLN. INFO.:			US 2000-232569P	P 20000914
			US 2000-251921P	P 20001207
			WO 2001-US28401	W 20010912

OTHER SOURCE(S): MARPAT 136:268115  
 AB Provided herein are novel and useful combretastatin A-4 prodrug salts that increase the soly. of combretastatin A-4, readily regenerate combretastatin A-4 in vivo under normal physiol. conditions, and which produce physiol. tolerable products as a result of the regeneration of combretastatin A-4.

IT 117048-59-6, Combretastatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combretastatin A-4 phosphate prodrug mono- and di-org. amine salts, mono- and di- amino acid salts, and mono- and di-amino acid ester salts)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



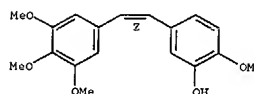
L24 ANSWER 40 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 41 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:180157 CAPLUS  
DOCUMENT NUMBER: 138:55697  
TITLE: Synthesis of disodium combretastatin A-4 3'-O-phosphate  
AUTHOR(S): Zhao, Huiping; Chen, Guorong; Li, Yuanhao  
CORPORATE SOURCE: Department of Fine Chemistry, East China University of Science + Technology, Shanghai, 200237, Peop. Rep. China  
SOURCE: Zhongguo Yiyao Gongye Zazhi (2001), 32(12), 531-532, 535  
CODEN: ZYGZEA; ISSN: 1001-8255  
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu  
DOCUMENT TYPE: Journal  
LANGUAGE: Chinese  
OTHER SOURCE(S): CASREACT 138:55697  
AB Disodium combretastatin A-4 3'-O-phosphate, a potent cancer growth and tubulin assembly inhibitor, was successfully synthesized via Wittig reaction between phosphonium bromide precursors synthesized from 3,4,5-trimethoxybenzyl alc. and silyl ether of isovanillin, desilylation, phosphorylation, cleavage of the phosphate ester, and salt formation in an overall yield of 32%.  
IT 117048-59-6P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



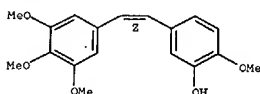
L24 ANSWER 42 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:112627 CAPLUS  
DOCUMENT NUMBER: 136:1303544  
TITLE: Protease-mediated fragmentation of p-amidobenzyl ethers: A new strategy for the activation of anticancer prodrugs  
AUTHOR(S): Toki, Brian E.; Cerveney, Charles G.; Wahl, Alan F.; Senter, Peter D.  
CORPORATE SOURCE: Seattle Genetics, Bothell, WA, 98021, USA  
SOURCE: Journal of Organic Chemistry (2002), 67(6), 1866-1872  
CODEN: JOCEAH; ISSN: 0022-3263  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-amidobenzyl ethers is described. Model studies were undertaken with the N-protected peptide benzylloxycarbonyl-valine-citrulline (2-val-cit), which was attached to the amino groups of p-amidobenzyl ether derivs. of 1-naphthol and N-acetylornithine. The amide bond that formed was designed for hydrolysis by cathepsin B, a protease assocd. with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the 2-val-cit-p-amidobenzyl ether of 1-naphthol underwent peptide bond hydrolysis with the rapid release of 1-naphthol. The aliph. 2-val-cit-p-amidobenzyl ether of N-acetylornithine also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylornithine. On the basis of these results, the phenolic anticancer drugs etoposide and combretastatin A-4 were attached to the 2-val-cit-p-amidobenzyl alc. through ether linkages, forming the peptide-drug derivs. Both compds. were stable in aq. buffers and serum and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chem. unmodified forms. The released drugs were 13-50 times more potent than were the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate deriv. of combretastatin A-4 was unstable in aq. environments and was as cytotoxic as combretastatin A-4. This result extends the use of the self-immolative p-amidobenzyl group for the fragmentation of arom. ethers and provides a new strategy for anticancer prodrug development.

IT 117048-59-6, Combretastatin A-4  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(protease-mediated fragmentation of p-amidobenzyl ethers: strategy for activation of anticancer prodrugs)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

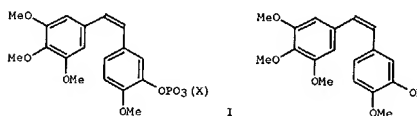
L24 ANSWER 43 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:72094 CAPLUS  
DOCUMENT NUMBER: 136:134622  
TITLE: Methods of synthesizing prodrugs of combretastatin A-4  
INVENTOR(S): Seyed, Faye; Gale, Jonathan; Haider, Reem; Hoare, John  
PATENT ASSIGNEE(S): Oligene, Inc., USA  
SOURCE: PCT Int. Appl., 41 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 200206279	A1	20020124	WO 2001-US22403	20010717
WO 200206279	C1	20020418		
WO 200206279	C2	20030403		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MP, MW, MX, MY, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TH, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AH, AE, BY, KG, KZ, MD, RU, TJ, TH  
KW: GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GN, GW, GM, ML, MR, NE, SN, TD, TG  
US 2002119951 A1 20020829 US 2001-908321 20010717  
PRIORITY APPL. INFO.: US 2000-218766P P 20000717

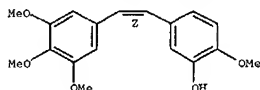
OTHER SOURCE(S): CASREACT 136:134622  
GI



AB The present invention discloses improved methods of synthesizing a phosphate ester of combretastatin A-4, such as I [X = H21, 22; Z1 = Na+, Li+; Z2 = Mg+2, Zn+2, Ca+2, Cs+2, imidazole, morpholine, etc.], and trans-isomers thereof. Thus, combretastatin A-4 (II) is reacted with dibenzylphosphite in the presence of carbon tetrabromide, or with 2,2,2-trichloroethyl phosphorodichloridate, to form a phosphate ester of combretastatin A-4 with protecting groups thereon.

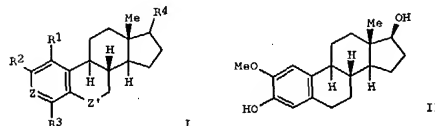
IT 117048-59-6P, Combretastatin A-4  
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(methods of synthesizing prodrugs of combretastatin A-4)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 43 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
Double bond geometry as shown.



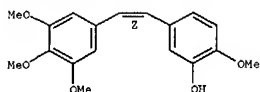
L24 ANSWER 44 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:11127 CAPLUS  
DOCUMENT NUMBER: 136:64669  
TITLE: Estrogenic compounds as antiangiogenic agents  
INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Gushman, Mark  
PATENT ASSIGNER(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.  
CODEN: USXXCO  
Patent  
DOCUMENT TYPE: English  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002002294	A1	20020103	US 2001-89702	20010705
PRIORITY APPLN. INFO.:			US 1997-59916P	P 19970924
			US 1998-154322	B1 19980916
OTHER SOURCE(S):		MARPAT 136:64669		
GI				

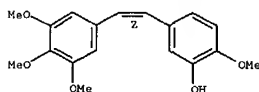


AB 2-Methoxyestradiol derivative, such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tpbond.CR, C-CH2, RCH=CH2, C.tpbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH), C=NOH, C=NOR5, CHC.tpbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polym. (IC50 = 3.6+-0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9+-0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.  
IT 117048-59-6, Combretastatin A-4  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (estrogenic compds. as antiangiogenic agents)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
Double bond geometry as shown.

L24 ANSWER 44 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



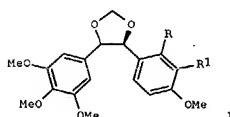
L24 ANSWER 45 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2002:9419 CAPLUS  
DOCUMENT NUMBER: 136:272793  
TITLE: Combination bacteriolytic therapy for the treatment of experimental tumors  
AUTHOR(S): Dang, Long H.; Bettegowda, Chetan; Huso, David L.; Kinzler, Kenneth W.; Vogelstein, Bert  
CORPORATE SOURCE: The Howard Hughes Medical Institute, Program in Cellular and Molecular Medicine, Division of Comparative Medicine, The Johns Hopkins School of Medicine, Baltimore, MD, 21231, USA  
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(26), 15155-15160  
CODEN: PNASAG; ISSN: 0027-8424  
PUBLISHER: National Academy of Sciences  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Current chemotherapeutic approaches for cancer are in part limited by the inability of drugs to destroy neoplastic cells within poorly vascularized compartments of tumors. We have here systematically assessed anaerobic bacteria for their capacity to grow expansively within avascular compartments of transplanted tumors. Among 26 different strains tested, one (Clostridium novyi) appeared particularly promising. We created a strain of C. novyi devoid of its lethal toxin (C. novyi-NT) and showed that i.v. injected C. novyi-NT spores germinated within the avascular regions of tumors in mice and destroyed surrounding viable tumor cells. When C. novyi-NT spores were administered together with conventional chemotherapeutic drugs, extensive hemorrhagic necrosis of tumors often developed within 24 h, resulting in significant and prolonged antitumor effects. This strategy, called combination bacteriolytic therapy (COBALT), has the potential to add a new dimension to the treatment of cancer.  
IT 117048-59-6, Combretastatin A4  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (combination antitumor therapy with toxin-devoid anaerobic bacteria spores and chemotherapeutic agents)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
Double bond geometry as shown.



L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:932999 CAPLUS  
 DOCUMENT NUMBER: 135:366721  
 TITLE: Antitubulin assembly and cell growth inhibitor  
 denominated "dioxostatin"  
 INVENTOR(S): Pettit, George R.; Lippert, John W., III  
 PATENT ASSIGNEE(S): Arizona Board of Regents, Arizona State University,  
 USA  
 SOURCE: PCT Int. Appl., 38 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001084929	A1	20011115	WO 2001-US14790	20010508
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1283672	A1	20030219	EP 2001-935147	20010508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
PRIORITY APPLN. INFO.:		US 2000-202770P P 20000509 WO 2001-US14790 W 20010508		

GI

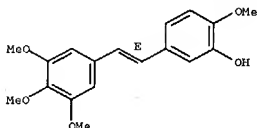


AB A new inhibitor of microtubule assembly (IC<sub>50</sub> 0.59 .mu.M); with antineoplastic properties, denominated "dioxostatin", has been synthesized and its effectiveness against human cancer and murine P388 lymphocytic leukemia cell lines demonstrated. Dioxostatin has the following structure (I).

IT 109971-63-3, Combretastatin A-1 109984-84-1  
 117048-59-6, Combretastatin A-4 117048-62-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antitubulin assembly and cell growth inhibitor denominated dioxostatin in relation to antineoplastic and antimicrobial activity)

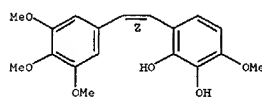
RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



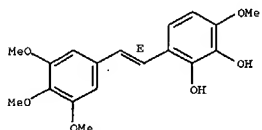
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 Double bond geometry as shown.



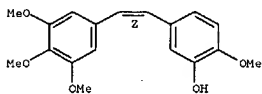
RN 109984-84-1 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



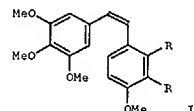
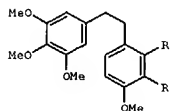
RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:798232 CAPLUS  
 DOCUMENT NUMBER: 135:344595  
 TITLE: Preparation of combretastatin A-1 phosphate and combretastatin B-1 phosphate prodrugs with increased solubility  
 INVENTOR(S): Pettit, George R.; Lippert, John W., III  
 PATENT ASSIGNEE(S): Arizona Board of Regents, A Body Corporate of the State of Arizona, Acting for and On Behalf of Arizona State University, USA  
 SOURCE: PCT Int. Appl., 41 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081355	A1	20011101	WO 2001-US13858	20010427
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1278758	A1	20030129	EP 2001-928978	20010427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
PRIORITY APPLN. INFO.:		US 2000-200395P P 20000427 WO 2001-US13858 W 20010427		
OTHER SOURCE(S):		CASREACT 135:344595		

GI



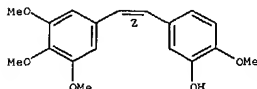
AB The present invention relates to the syntheses and structural elucidation of Combretastatin A1-Phosphate Prodrugs and Combretastatin B1-Phosphate Prodrugs and the use of those prodrugs in the treatment of neoplastic diseases. The prodrugs described herein have the structure: Combretastatin A-1 Phosphate Prodrug (I; R = F(O)(OMe)<sub>2</sub>, OPO<sub>3</sub> (e.g. Z = Li<sub>2</sub>, Cs, (morpholinium)<sub>2</sub>, (piperidinium)<sub>2</sub>); ED<sub>50</sub> < 0.0100 .mu.g/mL, P388 cell line for R = OPO<sub>3</sub>(Na<sub>2</sub>) and Combretastatin B-1 Phosphate Prodrug (II; ED<sub>50</sub> 0.335 .mu.g/mL, P388 cell line for R = OPO<sub>3</sub>(Na<sub>2</sub>)). Although no methods of prep. are claimed, the original synthesis of combretastatin A-1 was improved to allow an efficient scale-up procedure and procedures for diphosphorylation of combretastatin A-1 followed by conversions to various phosphate salts of combretastatin A-1 and its reduced form are described. Soly. and cancer cell line results are tabulated for many of the claimed compds.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (comparison of antitumor activity of combretastatin A-1 phosphate and



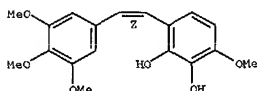
L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 combretastatin B-1 phosphate prodrugs to that of)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 109971-63-3P, Combretastatin A-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. and conversion to phosphate prodrugs with increased soly. and comparison of antitumor activity of combretastatin A-1 phosphate and combretastatin B-1 phosphate prodrugs to that of)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

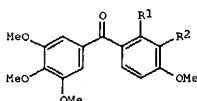


IT 109984-84-1P, (E)-2-(2,3-Dihydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of)  
 RN 109984-84-1 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

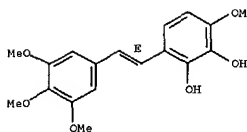
L24 ANSWER 48 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:798176 CAPLUS  
 DOCUMENT NUMBER: 135:331299  
 TITLE: Synthesis of hydroxyphenstatin and the prodrugs thereof as anticancer and antimicrobial agents  
 Pettit, George R.; Grealish, Matthew P.  
 INVENTOR(S): Arizona Board of Regents, A Body Corporate of the State of Arizona, Acting for and On Behalf of Arizona State University, USA  
 PATENT ASSIGNEE(S): FCT Int. Appl., 40 pp.  
 SOURCE: CODEN: FIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081288	A1	20011101	WO 2001-US13731	20010427
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1299337	A1	20030409	EP 2001-930892	20010427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
PRIORITY APPL. INFO.:		US 2000-200394P P 20000427		
		WO 2001-US13731 W 20010427		
OTHER SOURCE(S):		MARPAT 135:331299		
GI				



AB The benzophenone deriv. of combretastatin A-1, designated "hydroxyphenstatin" [I; R1 = R2 = OH] and X-hydroxyphenstatin diphosphate wherein X is selected from Na, Ca, Li and K in a pharmaceutically acceptable carrier, were prepd. for use as anticancer and antimicrobial agents. Thus, I [R1 = R2 = OPO(ONa)2 (II)] was prepd. via a multistep synthetic sequence starting from 3,4,5-trimethoxy benzaldehyde, o-vanillin, dibenzylphosphite and sodium iodide. The prepd. hydroxyphenstatin derivs. were tested for antitumor activity against a series of human cancer cells and murine P388 lymphocytic leukemia, antibacterial and antifungal activities (II GI50 = 0.0336 .mu.g/mL vs P388 cell line; IC50 = >40 .mu.M inhibition of tubulin polymn.; I [R1 = R2 = OPO(OCH2Ph)2] MIC = 50-100 .mu.g/dish).  
 IT 109971-63-3, Combretastatin A-1 117048-59-6,  
 Combretastatin A-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (inhibition of tubulin polymn. and inhibition of colchicine binding)  
 RN 109971-63-3 CAPLUS

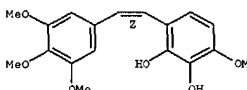
L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

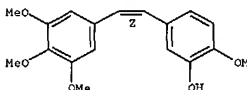
L24 ANSWER 48 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



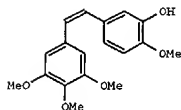
RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 49 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:795470 CAPLUS  
 DOCUMENT NUMBER: 136:102221  
 TITLE: Novel Syntheses of Cis and Trans Isomers of Combrebastatin A-4  
 AUTHOR(S): Gaukroger, Keira; Hadfield, John A.; Hopworth, Lucy A.; Lawrence, Nicholas J.; McGown, Alan T.  
 CORPORATE SOURCE: CRC Drug Development Group and CRC Radiochemical Targeting and Imaging Group, Paterson Institute for Cancer Research Christie Hospital NHS Trust, Manchester, M20 4BX, UK  
 SOURCE: Journal of Organic Chemistry (2001), 66(24), 8135-8138  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 136:102221  
 GI



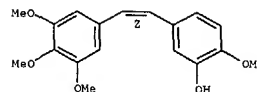
AB A high-yielding, two-step stereoselective synthesis of the anticancer drug (Z)-combrebastatin A-4 (I) was devised. The method uses the Perkin condensation of 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxybenzaldehyde followed by decarboxylation of the cinnamic acid intermediate using copper and quinoline. The iodine-catalyzed isomerization of the Z isomer I results in complete conversion to the E isomer. The Suzuki cross-coupling of an aryl boronic acid and vinyl bromide has also been successfully employed to produce both Z and E isomers of combrebastatin A-4 stereoselectively. Both methods are far superior to the current five-step Wittig synthesis in which both isomers are produced nonstereoselectively.

IT 117048-59-6P, Combrebastatin A-4  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of cis and trans isomers of combrebastatin A-4)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

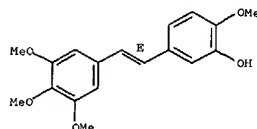
L24 ANSWER 49 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 117048-62-1P, Trans-combrebastatin A-4  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthesis of cis and trans isomers of combrebastatin A-4)

RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

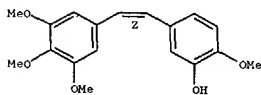
L24 ANSWER 50 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:750594 CAPLUS  
 DOCUMENT NUMBER: 136:395459  
 TITLE: Potent anti-metastatic activity of combrebastatin-A4  
 AUTHOR(S): Griggs, Jeremy; Brindle, Kevin M.; Metcalfe, James C.; Hill, Sally A.; Smith, Gerry A.; Beauregard, Daniel A.; Hesketh, Robin  
 CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK  
 SOURCE: International Journal of Oncology (2001), 19(4), 821-825  
 CODEN: IJONES; ISSN: 1019-6439  
 PUBLISHER: International Journal of Oncology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The requirement for tumor vascularization to permit the expansion of solid tumors beyond a threshold size of approx. 1 mm diam. has focussed attention on anti-vascular and anti-angiogenic agents for cancer therapy. Combrebastatin-A4 (cis-CA-4P) is a tubulin-binding agent that is cytotoxic for proliferating endothelial cells in vitro and causes anti-vascular effects in the established tumor vessels of some primary tumors. Preliminary data from Phase I clin. trials indicate that cis CA-4 may also be effective in targeting the vasculature of human tumors. As metastatic disease is the principal cause of mortality in cancer, we have investigated the effects of cis CA-4 on metastatic development using an in vivo model. We show that bolus or continuous administration of cis CA-4P results in potent inhibition of metastases derived from ectopic primary Lewis lung carcinomas in mice whereas the trans CA-4 isomer is without effect. These data further characterize the activity of CA-4 in vivo and suggest that the drug should be evaluated clin. as an anti-metastatic agent.

IT 117048-59-6, Combrebastatin-A4 117048-62-1, trans-Combrebastatin-A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anti-metastatic activity of combrebastatin-A4)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

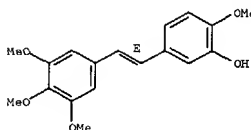
Double bond geometry as shown.



RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 50 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 51 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:628999 CAPLUS  
 DOCUMENT NUMBER: 135:344335  
 TITLE: The synthesis and tubulin binding activity of thiophene-based analogues of combretastatin A-4  
 AUTHOR(S): Flynn, B. L.; Flynn, G. P.; Hansel, E.; Jung, M. K.  
 CORPORATE SOURCE: The Faculties, Department of Chemistry, Australian National University, Canberra, 0200, Australia  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(17), 2341-2343  
 CODEN: BMCLER; ISSN: 0960-894X  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI

L24 ANSWER 51 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

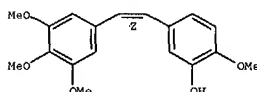
\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A no. of analogs of combretastatin A-4, contg. a thiophene ring interposed between the two Ph groups, have been prepd. The synthesis of these compds. employed a combination of palladium-mediated coupling and iodocyclization techniques. The thiophene compds. I, II (R1,R2,R3,R5 = OMe; R4 = OH, R6 = H; X = O), II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = OH, H), and II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = O) also represent non-benzofused analogs of some recently described tubulin binding benzo[b]thiophenes. The most active thiophene compds. identified in this study were I, II (R1,R2,R3,R5 = OMe; R4 = OH, R6 = H; X = O), and II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = OH, H). Overall they are less active than combretastatin A-4 but exhibit comparable activity to the most active of the benzo[b]thiophenes. A structure-activity relationship of these compds. is considered.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (synthesis and tubulin binding activity of thiophene-based analogs of combretastatin A-4)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-(2)-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

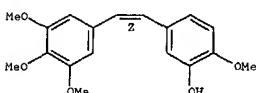
L24 ANSWER 52 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:483533 CAPLUS  
 DOCUMENT NUMBER: 136:318885  
 TITLE: Combretastatin A-4 and hyperthermia: a potent combination for the treatment of solid tumors  
 AUTHOR(S): Elkesdal, H. P.; Bjerkvig, R.; Mella, O.; Dahl, O.  
 CORPORATE SOURCE: Haukeland University Hospital, Department of Oncology, University of Bergen, Bergen, 5021, Norway  
 SOURCE: Radiotherapy and Oncology (2001), 60(2), 147-154  
 CODEN: RADONT; ISSN: 0167-8140  
 PUBLISHER: Elsevier Science Ireland Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Attacking tumor vasculature is a promising approach for the treatment of solid tumors. The tubulin inhibitor combretastatin A-4 disodium phosphate (CA-4) is a new vascular targeting drug which displays a low toxicity profile. We wanted to investigate how CA-4 influences tumor perfusion in the BT4An rat glioma and how the vascular targeting properties of CA-4 could be exploited to augment hyperthermic damage towards tumor vasculature. We used the 86RbCl extn. technique to assess how CA-4 influences tumor perfusion, and the tumor endothelium was examined for morphol. changes induced by the drug. We combined CA-4 (50 mg/kg i.p.) with hyperthermia (44, 60 min) at different time intervals to evaluate how therapy should be designed to affect tumor growth, and we studied the tumors histol. to assess tissue viability. We found that CA-4 induced a profound, but transient retn. in tumor perfusion 3-6 h postinjection. If hyperthermia was administered 3-6 h after injecting CA-4, massive hemorrhagic necrosis developed, and tumor responses were significantly enhanced compared to simultaneous administration of the two treatment modalities (P<0.005). CA-4 alone had no influence on tumor growth and failed to disrupt the vasculature of the BT4An solid tumors. Interestingly though, a mild endothelial edema was obsd. in some tumor areas 3 h after injecting CA-4. We conclude that the combination of CA-4 and hyperthermia is a potent therapeutic option for BT4An tumors, but the selection of adequate time intervals between CA-4 and hyperthermia are imperative to obtain tumor response.

IT 117048-59-6, Combretastatin A-4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combretastatin A-4 and hyperthermia combination for treatment of solid tumors)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-(2)-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

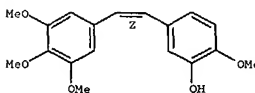
L24 ANSWER 53 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:379423 CAPLUS  
 DOCUMENT NUMBER: 135:189977  
 TITLE: Specific targeting of cytosine deaminase to solid tumors by engineered Clostridium acetobutylicum  
 AUTHOR(S): Theys, Jan; Landuyt, Willy; Muyts, Sandra; Van Mellaert, Lieke; Van Oosterom, Allan; Lambin, Philippe; Anne, Jozef  
 CORPORATE SOURCE: Laboratory of Bacteriology, Rega Institute for Medical Research, Louvain, B-3000, Belg.  
 SOURCE: Cancer Gene Therapy (2001), 8(4), 294-297  
 CODEN: CGTHEO; ISSN: 0929-1903  
 PUBLISHER: Nature America Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The presence of severe hypoxia and necrosis in solid tumors offers the potential to apply an anaerobic bacterial enzyme/prodrug approach in cancer treatment. In this context the apathogenic C. acetobutylicum was genetically engineered to express and secrete E. coli cytosine deaminase (CDase). Considerable levels of functional cytosine deaminase were detected in lysates and supernatants of recombinant C. acetobutylicum cultures. After administration of the recombinant Clostridium to rhabdomyosarcoma bearing rats used as a model, cytosine deaminase could be detected at the tumor site. Moreover, following administration of the vascular targeting agent combretastatin A-4 phosphate significantly increased levels of cytosine deaminase were detected at the tumor site as a consequence of enlarged tumor necrosis and subsequently improved growth of C. acetobutylicum. The results provide evidence for the potential application of Clostridium-based therapeutic protein transfer to tumors in anticancer therapy.

IT 117048-59-6, Combretastatin A4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (targeting of cytosine deaminase to solid tumors by engineered Clostridium acetobutylicum)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-(2)-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

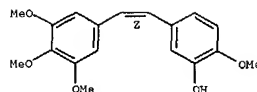
Double bond geometry as shown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 54 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:363661 CAPLUS  
 DOCUMENT NUMBER: 136:31366  
 TITLE: Combretestatin A4 prodrug study of effect on the growth and the microvasculature of colorectal liver metastases in a murine model  
 AUTHOR(S): Malcontenti-Wilson, Cathy; Muralidharan, Vijayaragavan; Skinner, Stewart; Christophi, Chris; Sherris, David; O'Brien, Paul E.  
 CORPORATE SOURCE: Alfred Hospital, Monash University Department of Surgery, Melbourne, 3181, Australia  
 SOURCE: Clinical Cancer Research (2001), 7(4), 1052-1060  
 CODEN: CCREF4; ISSN: 1078-0432  
 PUBLISHER: American Association for Cancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Combretestatin A4P (CA4P) is a prodrug that, in active form, binds to tubulin microtubules of capillary endothelial cells. Studies to date indicate it has significant activity as a specific tumor vascular targeting agent. The goals were to assess the effects of CA4P on tumor growth and microvasculature of colorectal liver metastases in the mouse model, using stereol. and histol. methods to measure tumor growth, and vascular corrosion casting and laser doppler flowmetry to assess effect on the microvasculature. Continuous s.c. infusion of CA4P produced a major reductn. in tumor growth. The percentage of the liver occupied by metastases decreased from 20.55±13.3% in controls to 7.46±5.99% in treated animals (P = 0.03). Ultrastructural study of tumor microvasculature after a single dose of CA4P revealed marked effects 1 h after treatment. There was loss of patent microvessels at the normal liver-tumor interface. Central microvascular d. was reduced, with constriction and tapering of vessels. CA4P appeared to cause no damage to normal liver tissue or vasculature. Tumor blood flow decreased from 37.6±13.9% in controls to 24.4±6.1% in tumors >5 mm in diam., 1 h after treatment with CA4P (P < 0.03). Quant. histol. of tissue at 6 and 24 h after CA4P treatment showed a significant increase in tumor necrosis (48.7±21% and 55.5±19% compared with controls, 20.6±8.8%; P = 0.01). Continuous infusion with CA4P causes marked reductn. in tumor vol. A single dose of CA4P causes major changes of the tumor microvasculature, reductn. of tumor blood flow, and increase in tumor necrosis. CA4P has a potential role in the management of patients with liver metastases.  
 IT 117048-59-6, Combretestatin A4  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combretestatin A4 prodrug study of effect on the growth and the microvasculature of colorectal liver metastases in a murine model)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

L24 ANSWER 54 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

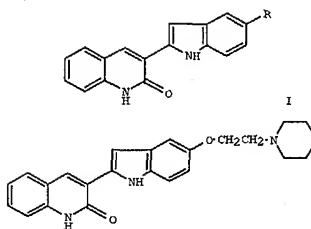


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

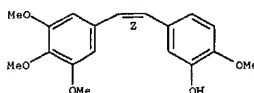
L24 ANSWER 55 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:300706 CAPLUS  
 DOCUMENT NUMBER: 134:326411  
 TITLE: Preparation of 3-(2-indolyl)quinoline-2-one derivatives as tyrosine kinase inhibitors  
 INVENTOR(S): Arrington, Kenneth L.; Bilodeau, Mark T.; Fraley, Mark E.; Hartman, George D.; Hoffman, William F.; Hungate, Randall W.; Kim, Yuntae  
 PATENT ASSIGNEE(S): Merck & Co., Inc., USA  
 SOURCE: PCT Int. Appl., 130 pp.  
 CODEN: PIXKXD  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029025	A2	20010426	WO 2000-US28625	20001016
WO 2001029025	A3	20011101		
W:	AS, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, EF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
BR 2000014843	A	20020611	BR 2000-14843	20001016
EP 1226136	A2	20020731	EP 2000-978230	20001016
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IS, SI, LT, LV, FI, NO, MK, CY, AL			
JP 2003512369	T2	20030402	JP 2001-531825	20001016
US 6306874	B1	20011023	US 2000-690598	20001017
NO 2002001820	A	20020523	NO 2002-1820	20020418
BG 106710	A	20030331	BG 2002-106710	20020516
PRIORITY APPLN. INFO.:			US 1993-160356P	19931019
			WO 2000-US28625	W 20001016
OTHER SOURCE(S):		MARPAT 134:326411		
GI				

L24 ANSWER 55 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

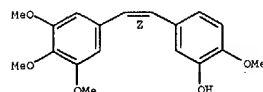


AB Title compds. [I: R = (CH3)2NCH2CH(CH3)CH2O, (CH3OCH2CH2)(C6H5CH2)NCH2CH2O, (CH3CH2)2NCH2CH2O, (CH3)(C6H5CH2)NCH2CH2CH2O, (CH3OCH2CH2)(HOOCCH2CH2)NCH2CH2O, (CH3OCH2CH2)(CH3SO2)NCH2, cycloalkylaminoalkyl, heterocyclylalkyl, etc.], stereoisomer, and pharmaceutically acceptable salts are prepd. and inhibit, regulate and/or modulate tyrosine kinase signal transduction. Title compds. are tested on VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001-5.0 μM. Pharmaceutical compns. and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, etc. are discussed. Thus, the title compd. II was prepd.  
 IT 117048-59-6, Combretestatin A-4  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (prepn. of 3-(2-indolyl)quinoline-2-one derivs. as tyrosine kinase inhibitors in compn. with other agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

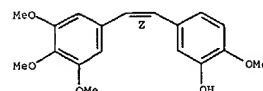


COc1cc(OC)c(OC)cc1/C=C/c2ccc(O)c(OC)c2

Double bond geometry as shown.



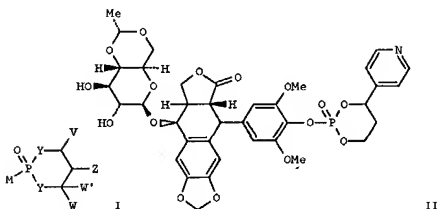
Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 59 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:185764 CAPLUS  
 DOCUMENT NUMBER: 134:237345  
 TITLE: Preparation of prodrugs for liver specific drug delivery  
 INVENTOR(S): Erion, Mark D.; Reddy, K. Raja  
 PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA  
 SOURCE: PCT Int. Appl., 160 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

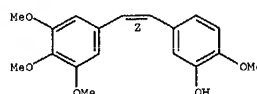
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001018013	A1	20010315	WO 2000-US24693	20000908
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TH, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1210354	A1	20020605	EP 2000-961694	20000908
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003508539	T2	20030304	JP 2001-522236	20000908
US 1999-153128P P 19990908				
WO 2000-US24693 W 20000908				
PRIORITY APPLN. INFO.: MARPAT 134:237345				
OTHER SOURCE(S): GI				



II

L24 ANSWER 59 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 AB Cyclic phosphoramidate prodrugs, such as I [M = pharmaceutical agent, such as camptothecin, paclitaxel, etc.; V, W, W' = H, alkyl, arylalkyl, aryl, heteroaryl, alkenyl, alkynyl, etc.; Z = H, hydroxymethyl, acyloxymethyl, etc.; YZ or VW = fused cyclic group; Y = O, NR, etc.; R = H, alkyl, etc.], were prepd. and formulated for pharmaceutical use for the delivery of drugs. Thus, prodrug II was prepd. in 48% yield from 1-(4-pyridyl)-1,3-propanediol, POC13, and etoposide. The prepd. prodrugs were tested for their resp. biol. activities, such as II being tested for activation in rat hepatocytes. The proposed uses of the prodrugs are to treat diseases that benefit from enhanced drug distribution to the liver and like tissues and cells that express cytochrome P 450, including hepatitis, cancer, liver fibrosis, malaria, other viral and parasitic infections, and metabolic diseases where the liver is responsible for the overprod. of the biochem. end product, e.g. glucose (diabetes); cholesterol, fatty acids and triglycerides (hyperlipidemia) (atherosclerosis) (obesity). These prodrugs are designed to enhance oral drug delivery, to prolong pharmacodynamic half-life of the drug, to achieve sustained delivery of the parent drug, to increase the therapeutic index of the drug, and to be useful in the delivery of diagnostic imaging agents to the liver.  
 IT 117048-59-6, Combretastatin A-4  
 R1: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (prepn. of prodrugs for liver specific drug delivery)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

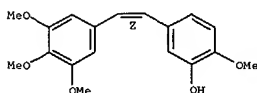
L24 ANSWER 60 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:152080 CAPLUS  
 DOCUMENT NUMBER: 135:146582  
 TITLE: Targeting tumor vasculature: The development of combretastatin A4  
 AUTHOR(S): Griggs, Jeremy; Metcalfe, James C.; Hesketh, Robin  
 CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK  
 SOURCE: Lancet Oncology (2001), 2(2), 82-87  
 CODEN: LOANEN; ISSN: 1470-2045  
 Lancet Publishing Group  
 PUBLISHER: Journal: General Review  
 DOCUMENT TYPE: English  
 LANGUAGE: English

AB A review with 37 refs. The requirement for neovascularization to permit the development of solid tumors beyond a threshold size, has focused attention on the therapeutic potential of agents that prevent angiogenesis. The multistep nature of angiogenesis presents several targets for intervention, including the inhibition of the endothelial-cell migration or proliferation normally assoc. with developing vessels. Compds. that damage established tumor vasculature are also of potential clin. use. We review the development of one such antivascular drug, combretastatin A4. This tubulin-binding agent was originally isolated from an African shrub, Combretum caffrum. The disodium combretastatin A4 phosphate prodrug is currently undergoing phase I clin. trials in the UK and USA. This review assesses the in vitro and in vivo data for combretastatin and the prodrug, and the preliminary data that have emerged from the phase I clin. trials.

IT 117048-59-6, combretastatin A4  
 R1: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

RN (targeting tumor vasculature: development of combretastatin A4)  
 CN 117048-59-6 CAPLUS  
 Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

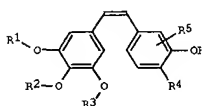
Double bond geometry as shown.



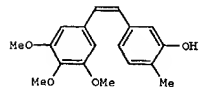
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:137169 CAPLUS  
 DOCUMENT NUMBER: 134:178403  
 TITLE: Preparation and use of cis-stilbenes with vascular damaging activity  
 INVENTOR(S): Davis, Peter David  
 PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
 SOURCE: PCT Int. Appl., 17 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TH, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809
US 1999-18912 A 19990812				
WO 2000-GB3067 W 20000809				
PRIORITY APPLN. INFO.: MARPAT 134:178403				
OTHER SOURCE(S): GI				



I

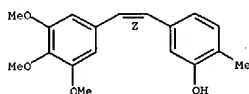


II

AB Compds. of formula I [wherein R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo]

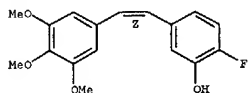
L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo are prep'd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prep'd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butylidimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. These compds. exhibit activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). Compds. I showed activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.  
 IT 288585-59-1P, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (prepn. and use of stilbenes with vascular damaging activity)  
 RN 288585-59-1 CAPLUS  
 CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



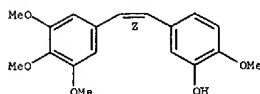
IT 326850-81-1P, (Z)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-82-2P, (Z)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-83-3P, (Z)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. and use of stilbenes with vascular damaging activity)  
 RN 326850-81-1 CAPLUS  
 CN Phenol, 2-fluoro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



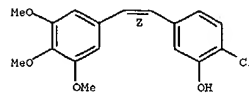
L24 ANSWER 62 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001125583 CAPLUS  
 DOCUMENT NUMBER: 134:348034  
 TITLE: Evaluation of combretastatin A-4 prodrug in a non-Hodgkin's lymphoma xenograft model: preclinical efficacy  
 AUTHOR(S): Nabha, Sanaa M.; Mohammad, Ramzi M.; Wall, Nathan R.; Dutcher, Julie A.; Salkini, Bashar M.; Pettit, George R.; Al-Katib, Ayad M.  
 CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, MI, 48201, USA  
 SOURCE: Anti-Cancer Drugs (2001), 12(1), 57-63  
 CODEN: ANTDEV; ISSN: 0959-4973  
 PUBLISHER: Lippincott Williams & Wilkins  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Combretastatin A-4 prodrug (CA4P) is a new antitubulin agent currently in phase I/II clin. trials against solid tumors. We have previously reported on the in vitro activity of CA4P against a panel of malignant human B-lymphoid cell lines. In this study, we investigated the antitumor and the antiangiogenic activity of CA4P in our diffuse large cell lymphoma WSU-DLCL2-SCID mouse model. WSU-DLCL2 cells (107) were injected s.c. into 5-wk-old female ICR-SCID mice. Tumor-bearing mice were treated at the CA4P max. tolerated dose (MTD) of 800 mg/kg in different dose/schedules. CA4P showed significant antitumor activity against this lymphoma model. Best results were seen when MTD was given in two and four divided doses (400 and 200 mg/kg, resp.). CA4P given in four divided doses (4.times.200 mg/kg) showed a log10 kill of 1.01, T/C of 11.7% and T-C of 12 days. Immunohistochem. staining using anti-CD31 antibody after 6, 24, 48 and 120 h treatment revealed a significant decrease in the no. of tumor blood vessels after 24 h (about 80%). Only the periphery of treated tumors revealed the presence of blood vessels. Morphol. examn. of the tumors after tetrachrome staining showed a necrotic center in tumors of CA4P-treated animals. New blood vessel formation was noted to emerge in tumor tissues as early as 48 h following a single dose of CA4P. The G2/M arrest obsd. in vitro was not detected in vivo indicating predominance of the antiangiogenic effects with regard to antitumor efficacy in vivo. We conclude that CA4P has antiangiogenic activity in this lymphoma model and the use of this agent should be explored clin. in the treatment of non-Hodgkin's lymphoma.  
 IT 117048-59-6, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (evaluation of combretastatin A-4 prodrug in a non-Hodgkin's lymphoma xenograft model)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



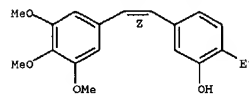
L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RN 326850-82-2 CAPLUS  
 CN Phenol, 2-chloro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



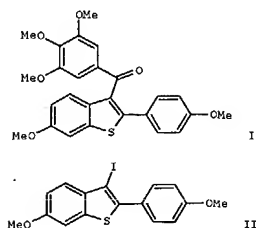
RN 326850-83-3 CAPLUS  
 CN Phenol, 2-ethyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 62 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 REFERENCE COUNT: 23  
 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

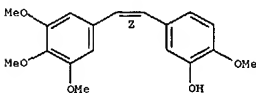
L24 ANSWER 63 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:85126 CAPLUS  
 DOCUMENT NUMBER: 134:295702  
 TITLE: A novel palladium-mediated coupling approach to 2,3-disubstituted benzo[b]thiophenes and its application to the synthesis of tubulin binding agents  
 AUTHOR(S): Flynn, Bernard L.; Verdier-Pinard, Pascal; Hamel, Ernest  
 CORPORATE SOURCE: Department of Chemistry The Faculties, Australian National University, Canberra, 0200, Australia  
 SOURCE: Organic Letters (2001), 3(5), 651-654  
 CODEN: ORLEF7; ISSN: 1523-7060  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 134:295702  
 GI



AB Flexible, convergent access to 2,3-disubstituted benzo[b]thiophenes, e.g. I, has been developed. The most concise approach involves sequential coupling of o-bromiodobenzenes with benzylmercaptan and zinc acetylides to give benzyl o-ethynylphenyl sulfides which react with iodine to give 3-iodobenzo[b]thiophenes, e.g. II, in a 5-endo-dig iodocyclization. These iodides can be further elaborated using palladium-mediated coupling and/or metalation techniques. This method has been applied to the synthesis of some novel tubulin binding agents. Several products were tested for their effects on tubulin polym., colchicine binding, and cytotoxicity in human Burkitt lymphoma.  
 IT 117048-59-6, Combretastatin A4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RIOL (Biological study)  
 (prepn. of disubstituted benzothiophenes via palladium-mediated coupling reactions and their tubulin polym./colchicine binding inhibiting-antitumor activities)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 64 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:135285 CAPLUS  
 DOCUMENT NUMBER: 135:70797  
 TITLE: Combretastatin A-4 and doxorubicin combination treatment is effective in a preclinical model of human medullary thyroid carcinoma  
 AUTHOR(S): Welkin, Barry D.; Ball, Douglas W.  
 CORPORATE SOURCE: Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA  
 SOURCE: Oncology Reports (2001), 8(1), 157-160  
 CODEN: OCREW; ISSN: 1021-335X  
 PUBLISHER: Oncology Reports  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Medullary thyroid carcinoma (MTC), both in patients and in preclin. models, is resistant to chemotherapy. In this study, we show that the anti-neovascular agent combretastatin A-4 phosphate prodrug (CAMP) in combination with doxorubicin was effective in curtailing tumor growth in a preclin. model of human MTC. This combination of combretastatin and doxorubicin extended the doubling time of established MTC tumors in nude mice to 29 days, compared to 12 days in untreated controls. This suggests that a combination of combretastatin and a cytotoxic chemotherapeutic agent may be an effective treatment for MTC.  
 IT 117048-59-6, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); RIOL (Biological study); USES (Uses)  
 (combretastatin A-4 and doxorubicin combination treatment is effective in a preclin. model of human medullary thyroid carcinoma)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

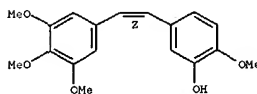
Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 63 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 INDEX NAME)

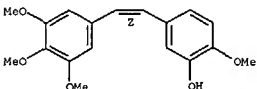
Double bond geometry as shown.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 65 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:844934 CAPLUS  
 DOCUMENT NUMBER: 134:86019  
 TITLE: Design, synthesis and cytotoxic activities of naphthyl analogs of combretastatin A-4  
 AUTHOR(S): Maya, Ana B. S.; Del Rey, Benedicto; De Clairac, Rafael; Pelaez Lamamier, Caballero, Esther; Barasoain, Isabel; Andreu, Jose Manuel; Medarde, Manuel  
 CORPORATE SOURCE: Laboratorio de Química Organica y Farmaceutica, Facultad de Farmacia, Universidad de Salamanca, Salamanca, 37007, Spain  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(22), 2549-2551  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 134:86019  
 AB The 3,4,5-trimethoxyphenyl and 3-hydroxy-4-methoxyphenyl rings of combretastatin A-4 are deemed optimal for its activity as antimitotic agent. The replacement of either one by a naphthalene ring results in compds. with a potency comparable to that of the parent compd. These results show that the naphthalene ring is a good surrogate for the 3,4,5-trimethoxyphenyl or the 3-hydroxy-4-methoxyphenyl rings of combretastatin A-4 and that neither of them is essential for the antitumor activity.  
 IT 117048-59-6, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); RIOL (Biological study); USES (Uses)  
 (prepn. of naphthyl analogs of combretastatin A-4 as antitumor agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

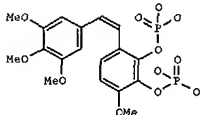


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L24 ANSWER 66 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:774929 CAPLUS  
 DOCUMENT NUMBER: 134:125660  
 TITLE: The Interaction of the B-ring of Colchicine with .alpha.-Tubulin: A Novel Footprinting Approach  
 AUTHOR(S): Chaudhuri, Asish R.; Seetharamulu, P.; Schwarz, Patricia M.; Hausheer, F. H.; Luduea, Richard F.  
 CORPORATE SOURCE: Department of Biochemistry, University of Texas Health Science Center at San Antonio, TX, 78229, USA  
 SOURCE: Journal of Molecular Biology (2000), 303(5), 679-692  
 CODEN: JMOBAK ISSN: 0022-2836  
 PUBLISHER: Academic Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Tubulin, the major structural component of the microtubules, participates actively in mitotic spindle formation and chromosomal organization during cell division. Tubulin is the major target for a variety of anti-mitotic drugs. Some of the drugs, such as Vinca alkaloids and taxol, are routinely used for cancer chemotherapy. It is unfortunate that the authors knowledge of the binding sites on tubulin of these drugs is limited because of lack of a useful and appropriate tool. The photoaffinity labeling approach is the major technique available at present to detect the binding sites of drugs on tubulin. This method, however, has several limitations. First, only part of the binding site can be identified, namely, the residues which react with the photoaffinity label. Second, there are regions of tubulin which are not at the binding site but are affected by the binding of the drug; these regions can not be detected by the photoaffinity labeling approach. The third, and perhaps most serious, limitation is that the traditional approach can detect areas which have nothing to do with the binding of the ligand but which are within a certain distance of the binding site, that distance being less than the length of the photoreactive moiety attached to the ligand. There has been a great deal of controversy on the localization of the binding site of colchicine on tubulin, with some reports suggesting that the binding site is on .alpha. and some supporting a binding site on .beta.. Colchicine also has significant effects on tubulin conformation, but the regions which are affected have not been identified. The authors have attempted here to address these questions by a novel "footprinting" method by which the drug-binding sites and as well as the domain of tubulin affected by drug-induced conformational changes could be detd. Here, the authors report for the first time that the interaction of the B-ring of colchicine with the .alpha.-subunit affects a domain of tubulin which appears to be far from its binding site. This domain includes the cysteine residues at positions 295, 305, 315 and 316 on .alpha.-tubulin; these residues are located well away from the .alpha./beta. interface where colchicine appears to bind. This is correlated with the stabilizing effect of colchicine on the tubulin mol. Furthermore, the authors also found that the B-ring of colchicine plays a major role in the stability of tubulin while the A and the C-rings have little effect on it. Our results therefore, support a model whereby colchicine binds at the .alpha./beta. interface of tubulin with the B-ring on the .alpha.-subunit and the A and the C-rings on the .beta.-subunit. (c) 2000 Academic Press.  
 IT 117048-59-6, Combretastatin A-4  
 RI: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (interaction of B-ring of colchicine with .alpha.-tubulin using novel footprinting approach to detn. drug binding)

L24 ANSWER 67 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:757705 CAPLUS  
 DOCUMENT NUMBER: 134:51116  
 TITLE: Antineoplastic agents 429. Syntheses of the combretastatin A-1 and combretastatin B-1 prodrugs  
 AUTHOR(S): Pettit, George R.; Lippert, John W., III  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Anti-Cancer Drug Design (2000), 15(3), 203-216  
 CODEN: ACDEUA ISSN: 0266-9536  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI

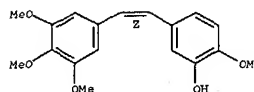


AB The original synthesis of combretastatin A-1 was modified to allow an efficient scale-up procedure for obtaining this antineoplastic stilbene. Subsequent conversion to a useful prodrug was accomplished by diphosphorylation, with in situ formation of dibenzylchlorophosphite, followed by cleavage of the benzyl ester protecting groups with trimethylsilylhydrosilane. The phosphoric acid intermediate was treated with sodium methoxide to complete a practical route to the sodium phosphate prodrug (I). Selective hydrogenation of phosphate deriv. and treatment of the product with sodium methoxide led to combretastatin B-1 prodrug. The phosphoric acid precursor of prodrug I was employed in a parallel series of reactions to produce a selection of metal and ammonium cation prodrug candidates. Each of the phosphate salts was evaluated from the perspective of relative soly. behavior and cancer cell growth inhibition. The sodium phosphate prodrug I was selected for detailed antineoplastic studies.  
 IT 109971-63-3P, Combretastatin A-1  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

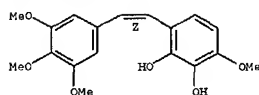
L24 ANSWER 66 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



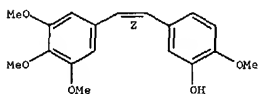
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 67 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



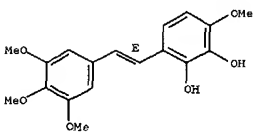
IT 117048-59-6, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 109984-84-1P  
 RI: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)  
 RN 109984-84-1 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 68 OF 157 CAPLUS COPYRIGHT 2003 ACS

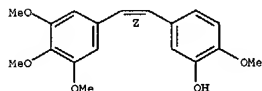
ACCESSION NUMBER: 2000:754871 CAPLUS  
 DOCUMENT NUMBER: 134:260980  
 TITLE: Combretastatins: novel vascular targeting drugs for improving anticancer therapy. Combretastatins and conventional therapy  
 AUTHOR(S): Horsman, M. R.; Murata, R.; Breidahl, T.; Nielsen, F. U.; Maxwell, R. J.; Stodkild-Jorgensen, H.; Overgaard, J.  
 CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital and MR-Centre, Aarhus, Den.  
 SOURCE: Advances in Experimental Medicine and Biology (2000), 476(Angiogenesis: From the Molecular to Integrative Pharmacology), 311-323  
 CODEN: AEMBAP; ISSN: 0065-2598  
 PUBLISHER: Kluwer Academic/Plenum Publishers  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB This study investigated the potential of combretastatin A-4 disodium phosphate (CA4DP) to induce vascular effects in a C3H mouse mammary carcinoma and studied whether the antitumor response could be improved by combining the drug with conventional anticancer therapies. CA4DP (250 mg/kg) decreased tumor perfusion within 30 min after injection and maintained this effect for several hours, although there was a return to normal by 24 h. Similar changes were seen in the bioenergetic and oxygenation status of the tumors. The drug also increased tumor necrosis and had a small inhibitory effect on tumor growth. It was also able to enhance the tumor response to radiation and hyperthermia, when given at the same time or 30 min after radiation and hyperthermia, resp. Giving the drug 1 h after cisplatin injection resulted only in a tumor response that was no greater than additive. These results confirm the antivascular effects of CA4DP and demonstrate its potential to enhance the antitumor activity of conventional therapy.

IT 117048-59-6, Combretastatin A4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antitumor activity of combretastatin A4 and its interaction with radiotherapy and hyperthermia)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 68 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 69 OF 157 CAPLUS COPYRIGHT 2003 ACS

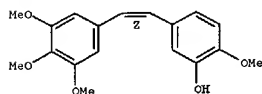
ACCESSION NUMBER: 2000:726998 CAPLUS  
 DOCUMENT NUMBER: 134:29214  
 TITLE: Natural organic compounds that affect microtubule functions: syntheses and structure-activity relationships of Combretastatins, Curacin A and their analogs as the Colchicine-site ligands on tubulin  
 AUTHOR(S): Iwasaki, Shigeo; Shirai, Ryuichi  
 CORPORATE SOURCE: Research Center for Biological Function, Kitasato Institute, Tokyo, 108-8642, Japan  
 SOURCE: Yakugaku Zasshi (2000), 120(10), 875-890  
 CODEN: YKZZAJ; ISSN: 0031-6903  
 PUBLISHER: Pharmaceutical Society of Japan  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: Japanese

AB A review with 38 refs. Microtubules (MT) are cylindrical polymers of the protein tubulin (TN) .alpha.,.beta.-heterodimer, and are known to be the main component of spindles in mitotic app. of eucaryotic cells. MT are also involved in many other basic and essential cell functions. There are a no. of natural and synthetic compds. that interfere with MT function to cause the mitotic arrest of eucaryotic cells. Such antimitotic agents show a broad biol. activity, and can be used for medicinal and agrochem. purposes. On the other hand, they are important also as the biochem. tools for understanding the dynamics of MT network. Most of such antimitotic agents, with a few exceptions, bind to .beta.-TN. Among them, colchicine (CLC), vinblastine and taxol have played major roles in practical uses as well as in biochem. studies of MT functions. They all bind to .beta.-TN but their binding sites are different. The authors have worked on a variety of antimitotic agents that bind to either of colchicine-site, vinblastine-site and taxol-site, in discovery, structures, biol. actions and/or interactions with TN. In this paper, the results of the authors' studies on CLC-site ligands were summarized; (1) synthetic analogs of combretastatin A-4 (CBS A-4), isolated as a cytotoxic compd. produced by a species of South African tree Combretum caffrum, (2) curacin A (CU-A), a cytotoxic metabolite of a marine cyanobacteria Lyngbya majuscula, and its related compds. Interactions of these compds. with TN were studied and structure-activity relationships of these two classes of compds. were discussed.

IT 117048-59-6DP, Combretastatin A-4, analogs  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (natural org. compds. having effect on microtubule functions and synthesis and structure-activity relationships of combretastatins, curacin A and analogs as colchicine-site ligands on tubulin)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

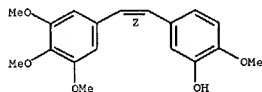
Double bond geometry as shown.



L24 ANSWER 69 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 70 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:658688 CAPLUS  
 DOCUMENT NUMBER: 134:52722  
 TITLE: Synthesis and biological evaluation of aryl azide derivatives of combretastatin A-4 as molecular probes for tubulin  
 AUTHOR(S): Pinney, K. G.; Mejia, M. P.; Villalobos, V. M.; Rosenquist, B. E.; Pettit, G. R.; Verdier-Pinard, P.; Hamel, E.  
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, Baylor University, Waco, TX, 76798-7348, USA  
 SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(10), 2417-2425  
 CODEN: RMECEP; ISSN: 0958-0896  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 134:52722  
 AB Two new aryl azides, (Z)-1-(3'-azido-4'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)ethene [I] and (Z)-1-(4'-azido-3'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)ethene [II], modeled after the potent antitumor, antimitotic agent combretastatin A-4 (CA-4), have been prepd. by chem. synthesis as potentially useful photoaffinity labeling reagents for the colchicine site on  $\beta$ -tubulin. Aryl azide I, in which the 3'-hydroxyl group of CA-4 is replaced by an azido moiety, demonstrates excellent in vitro cytotoxicity against human cancer cell lines (NCI 60 cell line panel, av. GI50=4.07.times.10<sup>-8</sup> M) and potent inhibition of tubulin polymn. (IC50=1.4 $\pm$ 0.1  $\mu$ M). The 4'-azido analog II has lower activity (NCI 60 cell line panel, av. GI50=2.28.times.10<sup>-6</sup> M, and IC50=5.2 $\pm$ 0.2  $\mu$ M for inhibition of tubulin polymn.), suggesting the importance of the 4'-methoxy moiety for interaction with the colchicine binding site on tubulin. These CA-4 aryl azide analogs also inhibit binding of colchicine to tubulin, as does the parent CA-4, and therefore these compds. are excellent candidates for photoaffinity labeling studies.  
 IT 117048-59-6, Combretastatin A4 117048-59-6D, Combretastatin A-4, analogs  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (synthesis and biol. evaluation of aryl azide deriva. of combretastatin A-4 as mol. probes for tubulin)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

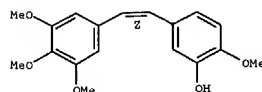
Double bond geometry as shown.



RN 117048-59-6 CAPLUS

L24 ANSWER 71 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:656267 CAPLUS  
 DOCUMENT NUMBER: 133:246908  
 TITLE: Antiangiogenic treatment of human non-small cell lung cancer (NSCLC) in a murine xenotransplant model  
 AUTHOR(S): Bohle, A. S.; Dohrmann, P.; Kalthoff, H.; Henne-Bruns, D.  
 CORPORATE SOURCE: Klinik für Allgemeine Chirurgie und Thoraxchirurgie, Arbeitsgruppe Molekulare Onkologie, Christian-Albrechts-Universität zu Kiel, Kiel, 24105, Germany  
 SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (2000) 403-407  
 CODEN: CFKA7; ISSN: 0303-6227  
 PUBLISHER: Springer-Verlag  
 DOCUMENT TYPE: Journal  
 LANGUAGE: German  
 AB The aim of this study was to evaluate the biol. effect of the antiangiogenic agent CA4PD on human non-small cell lung cancer (NSCLC) in a murine xenotransplant model. Human NSCLC were treated by systemic administration of the antiangiogenic agent CA4PD in a heterotopic, s.c. tumor model and a lethal, ortho-topic human lung cancer tumor model. Systemic administration of the agent CA4PD resulted, in s.c. induced tumors, in a redn. of tumor growth. After ortho-topic tumor induction in the lung, survival was prolonged by 29% and 35%, resp. Systemic antiangiogenic treatment of human NSCLC in the murine xenotransplant model is effective in reducing tumor proliferation and prolonging animal survival.  
 IT 117048-59-6, Combretastatin-A4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (prodrug; antiangiogenic treatment of human non-small cell lung cancer in a xenotransplant model with CA4PD)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

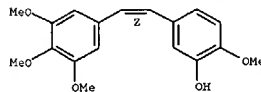
Double bond geometry as shown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 70 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

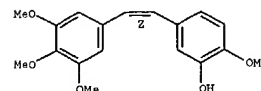
Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 72 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:647330 CAPLUS  
 DOCUMENT NUMBER: 134:141436  
 TITLE: Combretastatin A-4 prodrug: A potent inhibitor of malignant hemangioendothelioma cell proliferation  
 AUTHOR(S): Bohle, A. S.; Leuchner, I.; Kalthoff, H.; Henne-Bruns, D.  
 CORPORATE SOURCE: Department of General Surgery and Thoracic Surgery, Christian-Albrechts-Universität, Kiel, 24105, Germany  
 SOURCE: International Journal of Cancer (2000), 87(6), 838-843  
 CODEN: IJCNRA; ISSN: 0020-7136  
 PUBLISHER: Wiley-Liss, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Anti-vascular treatment by targeting proliferating endothelial cells has become a promising option in anti-neoplastic therapy. Combretastatin A-4 prodrug (CA-4PD) has been identified as a selective inhibitor of endothelial cell proliferation, acting by the interruption of microtubule assembly. In this study, the effect of CA-4PD on proliferating endothelial cells derived from a primary tumor of the vascular endothelium was investigated in vitro and in vivo. In vitro, CA-4PD was an effective inhibitor of endothelial cell proliferation in a time- and dose-dependent manner, displaying a certain selectivity toward endothelial cells in comparison to proliferating fibroblasts. Anal. of DNA profiles by FACS revealed an increasing proportion of cells arrested in the G2 cell-cycle phase with correlation to the duration of drug exposure. A decrease in cell viability correlated with duration of drug exposure, whereas FACS anal., DNA fragmentation assay, and DNA gel electrophoresis failed to demonstrate that DNA fragmentation was indicative of apoptosis up to 48 h of continued drug exposure. In vivo, CA-4PD induced excessive regressive alterations in exptl. allotransplanted hemangioendotheliomas within 24 h after singular i.p. injection of 100 mg CA-4PD/kg body wt. This represented less than one-tenth of the max. tolerated dose. In conclusion, our findings characterize CA-4PD as a potent inhibitor of malignant endothelial cell proliferation in vitro, effecting arrest of proliferating cells in the G2 cell-cycle phase with subsequent cell death on a pathway different from apoptosis. In vivo, CA-4PD induces extensive intratumoral cell loss within 24 h following systemic administration, suggesting a synergistic effect of direct cell killing and the induction of vascular shutdown.  
 IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combretastatin A-4 prodrug, a potent inhibitor of malignant hemangioendothelioma cell proliferation)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



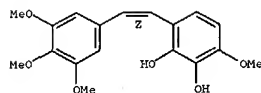
L24 ANSWER 72 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 REFERENCE COUNT: 21  
 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 73 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:592560 CAPLUS  
 DOCUMENT NUMBER: 133:198575  
 TITLE: Compositions and methods for use in targeting vascular destruction  
 INVENTOR(S): Péro, Ronald W.; Sherris, David  
 PATENT ASSIGNEE(S): Oxigene, Inc., USA  
 SOURCE: PCT Int. Appl., 36 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WQ 2000048606	A1	20000824	WO 2000-US3996	20000216
W:	AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2358925	AA	20000824	CA 2000-2358925	20000216
EP 1152764	A1	20011114	EP 2000-914606	20000216
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002537262	T2	20021105	JP 2000-599398	20000216
US 6538038	B1	20030325	US 2000-505402	20000216
US 2003109500	A1	20030612	US 2002-218833	20020814
PRIORITY APPL. INFO.:			US 1999-120478P	P 19990218
			US 2000-505402	A1 20000216
			WO 2000-US3996	W 20000216

OTHER SOURCE(S): MARPAT 133:198575  
 AB Treatment of warm-blooded animals having a tumor or non-malignant hypervascularization, by administering a sufficient amt. of a cytotoxic agent formulated into a phosphate prodrug form having substrate specificity for microvessel phosphatases, so that microvessels are destroyed preferentially over other normal tissues, because the less cytotoxic prodrug form is converted to the highly cytotoxic dephosphorylated form.  
 IT 109971-63-3  
 RL: RAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (prodrugs for use in targeting vascular destruction)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

L24 ANSWER 73 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

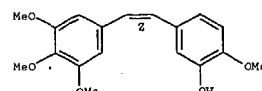


REFERENCE COUNT: 1  
 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 74 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:592548 CAPLUS  
 DOCUMENT NUMBER: 133:177486  
 TITLE: Preparation of substituted stilbene compounds with vascular damaging activity  
 INVENTOR(S): Davis, Peter David  
 PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
 SOURCE: PCT Int. Appl., 31 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WQ 2000048590	A1	20000824	WO 2000-GB503	20000215
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1154767	A1	20011121	EP 2000-903824	20000215
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPL. INFO.:			GB 1999-3403	A 19990216
			WO 2000-GB503	W 20000215

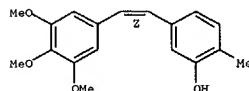
OTHER SOURCE(S): MARPAT 133:177486  
 AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyl)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing C26 or S18 tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.  
 IT 117048-59-6  
 RL: RCT (Reactant); RACT (Reactant or reagent) (prepn. of substituted stilbene compds. with vascular damaging activity)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.



IT 288585-59-1P

L24 ANSWER 74 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT.  
 (Reactant or reagent)  
 (prepn. of substituted stilbene compds. with vascular damaging  
 activity)  
 RN 288586-59-1 CAPLUS  
 CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 75 OF 157 CAPLUS COPYRIGHT 2003 ACS

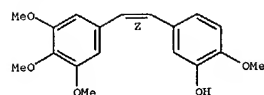
ACCESSION NUMBER: 2000:503373 CAPLUS  
 DOCUMENT NUMBER: 133:202672  
 TITLE: Effects of combretastatin A-4 prodrug against a panel  
 of malignant human B-lymphoid cell lines  
 AUTHOR(S): Nabha, Sanaa M.; Wall, Nathan R.; Mohammad, Ramzi M.;  
 Pettit, George R.; Al-Katib, Ayad M.  
 CORPORATE SOURCE: Division of Hematology and Oncology, Karmanos Cancer  
 Institute, School of Medicine, Wayne State University,  
 Detroit, MI, 48201, USA  
 SOURCE: Anti-Cancer Drugs (2000), 11(5), 385-392  
 CODEN: ANTDEV; ISSN: 0959-4973  
 PUBLISHER: Lippincott Williams & Wilkins  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Combretastatin A-4 (CA-4) is one of a family of compds. isolated from the

South African willow tree Combretum caffrum. CA-4 was active against  
 murine melanoma and a variety of other human solid tumors. For the first  
 time, we report the effect of CA-4 against a panel of malignant human  
 B-lymphoid cell lines [early pre-B acute lymphoblastic leukemia (Reh),  
 diffuse large cell lymphoma (WSU-DLCL2), chronic lymphocytic leukemia  
 (WSU-CLL) and Waldenstrom's macroglobulinemia (WSU-WM)]. Our results  
 indicate, using the prodrug form of CA-4, a concn.-dependent growth  
 inhibition in all tested cell lines, although WSU-DLCL2 was more  
 sensitive. Exposure to 4 nM CA-4 for 96 h induced 77% growth inhibition  
 in Reh, 86% in WSU-CLL and 92% in WSU-WM. When used against the WSU-DLCL2  
 cell line, this same concn. of CA-4 was completely toxic. Morphol. exam.  
 showed CA-4 induced the formation of giant, multinucleated cells, a  
 phenomenon commonly found in mitotic catastrophes. Only minimal nos. of  
 cells showing characteristics of apoptosis were detected. In WSU-DLCL2  
 cells, CA-4 (3 nM) induced the highest apoptosis (51) after 48 h, while  
 the percentage of dead cells was approx. 47%. Exposure of Reh, WSU-CLL,  
 WSU-WM and WSU-DLCL2 cells for 24 h to 5 nM CA-4 induced 19, 28, 57 and  
 75% G2/M arrest, as detd. by flow cytometry, resp. Based on these  
 preliminary studies, we believe that mitotic catastrophe is the  
 predominant mechanism by which CA-4 induces cell death rather than  
 apoptosis. Further studies to elucidate the mechanisms of CA-4 activity  
 in vitro and in vivo are currently under investigation in our lab.

IT RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)  
 (effects of combretastatin A-4 prodrug against a panel of malignant  
 human B-lymphoid cell lines)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 75 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

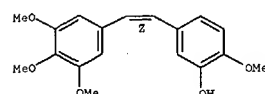
L24 ANSWER 76 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:454837 CAPLUS  
 DOCUMENT NUMBER: 133:234061  
 TITLE: Comparative molecular field analysis of colchicine  
 inhibition and tubulin polymerization for  
 combretastatins binding to the colchicine binding site  
 on .beta.-tubulin  
 AUTHOR(S): Brown, M. L.; Rieger, J. M.; Macdonald, T. L.  
 CORPORATE SOURCE: Chemistry Department, University of Virginia,  
 Charlottesville, VA, 22904-4319, USA  
 SOURCE: Biorganic & Medicinal Chemistry (2000), 8(6),  
 1433-1441  
 CODEN: BMCEP; ISSN: 0968-0896  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB A mol. modeling study using Comparative Mol. Field Anal. (CoMFA) was

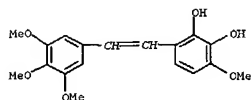
undertaken to develop a predictive model for combretastatin binding to the  
 colchicine binding site of tubulin. Furthermore, we examd. the potential  
 contribution of lipophilicity (log P) and mol. dipole moment and were  
 unable to correlate these properties to the obsd. biol. data. In this  
 study we first confirmed that tubulin polymn. inhibition (IC50) correlated  
 (R2=0.92) with [3H]colchicine displacement. Although these data  
 correlated quite well, we developed two independent models for each set of  
 data to quantify structural features that may contribute to each biol.  
 property independently. To develop our predictive model we first examd. a  
 series of mol. alignments for the training set and ultimately found that  
 overlaying the resp. trimethoxyphenyl rings (A ring) of the analogs  
 generated the best correlated model. The CoMFA yielded a cross-validated  
 R2=0.41 (optimum no. of components equal to 5) for the tubulin polymn.  
 model and an R2=0.38 (optimum no. of components equal to 5) for  
 [3H]colchicine inhibition. Final non-cross-validation generated models  
 for tubulin polymn. (R2 of 0.93) and colchicine inhibition (R2 of 0.91).  
 These models were validated by predicting both biol. properties for  
 compds. not used in the training set. These models accurately predicted  
 the IC50 for tubulin polymn. with an R2 of 0.88 (n=6) and those of  
 [3H]colchicine displacement with an R2 of 0.80 (n=7). This study  
 represents the first predictive model for the colchicine binding site over  
 a wide range of combretastatin analogs.

IT 117048-59-6, Combretastatin A4 283301-40-3  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological  
 process); BSU (Biological study, unclassified); PRP (Properties); BIOL  
 (Biological study); PROC (Process)  
 (comparative mol. field anal. of colchicine inhibition and tubulin  
 polymn. for combretastatins binding to the colchicine binding site on  
 .beta.-tubulin)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.

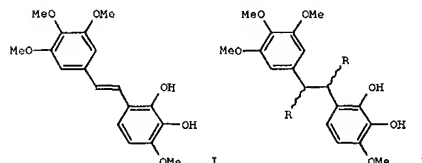


L24 ANSWER 76 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RN 293301-40-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI)  
 (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

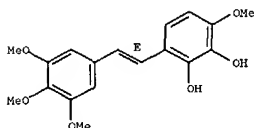
L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:443011 CAPLUS  
 DOCUMENT NUMBER: 133:207722  
 TITLE: Antineoplastic Agents 440. Asymmetric Synthesis and Evaluation of the Combretastatin A-1 SAR Probes (1S,2S)- and (1R,2R)-1,2-Dihydroxy-1-(2',3'-dihydroxy-4'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)-ethane  
 AUTHOR(S): Pettit, George R.; Lippert, John W., III; Herald, Delbert L.; Hamel, Ernest; Pettit, Robin K.  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Journal of Natural Products (2000), 63(7), 969-974  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB The synthetic (E)-isomer (I) of natural combretastatin A-1 isolated from the African bushwillow *Combretum caffrum* was the focus of chiral hydroxylation (Sharpless) reactions as part of a structure-activity relationship study. The resulting (R,R)- (II; R = .alpha.-OH) (III) and (S,S)-diols II (R = .beta.-OH) (IV) and synthetic intermediates were evaluated against a series of cancer cell lines, microorganisms, and tubulin. Chiral diols III and IV showed increased activity against the P-388 murine lymphocytic leukemia cell line with ED50 values of 3.9 and 2.9 .mu.g/mL, resp., when compared to the precursor (E)-stilbene I. In contrast, I exhibited more potent antibiotic activity than the chiral diols, III and IV. Both diols, III and IV, displayed less cancer cell growth inhibition and less antibiotic activity than did natural combretastatin A-1 (P-388 ED50 0.25 .mu.g/mL).

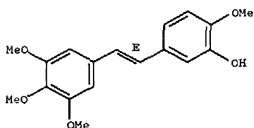
IT 109984-84-1 117048-62-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (antimicrobial activity of, in structure activity relationship study of the combretastatin A1 SAR probes)  
 RN 109984-84-1 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 Double bond geometry as shown.



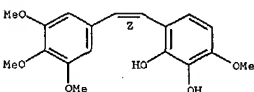
RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 109971-63-3 117048-59-6  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (cytotoxicity, antimicrobial and tubulin polymn. inhibitory activity of, in structure activity relationship study of the combretastatin A1 SAR probes)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

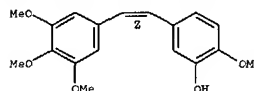
Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

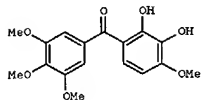
Double bond geometry as shown.

L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 78 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:425859 CAPLUS  
 DOCUMENT NUMBER: 133:207717  
 TITLE: Antineoplastic Agents. 443. Synthesis of the Cancer Cell Growth Inhibitor Hydroxyphenstatin and Its Sodium Diphosphate Prodrug  
 AUTHOR(S): Pettit, George R.; Grealish, Matthew P.; Herald, Delbert L.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Journal of Medicinal Chemistry (2000), 43(14), 2731-2737  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI

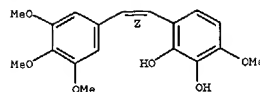


AB A structure-activity relationship (SAR) study of the South African willow tree (*Combretum cafrum*) antineoplastic constituent combretastatin A-4 led to the discovery of a potent cancer cell growth inhibitor designated phenstatin. This benzophenone deriv. of combretastatin A-4 showed remarkable antineoplastic activity, and the benzophenone deriv. of combretastatin A-1 was therefore synthesized. The benzophenone, designated hydroxyphenstatin (I), was synthesized by coupling of a protected bromobenzene and a benzaldehyde to give the benzhydrol with subsequent oxidn. to the ketone. Hydroxyphenstatin was converted to the sodium phosphate prodrug by a dibenzyl phosphite phosphorylation and subsequent benzyl cleavage. While hydroxyphenstatin I was a potent inhibitor of tubulin polymn. with activity comparable to that of combretastatin A-1, the phosphorylated deriv. of I was inactive.

IT 109971-63-3, Combretastatin A-1 117048-59-6,  
 Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (synthesis of cancer cell growth inhibitor hydroxyphenstatin and sodium diphosphate prodrug)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

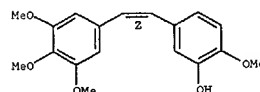
Double bond geometry as shown.

L24 ANSWER 78 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

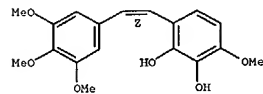
L24 ANSWER 79 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:402212 CAPLUS  
 DOCUMENT NUMBER: 134:190683  
 TITLE: Bioactive compounds from *Combretum erythrophyllum*. [Erratum to document cited in CA132:345465]  
 AUTHOR(S): Schwikard, Sianne; Zhou, Bing-Nan; Glass, Thomas E.; Sharp, Jessica L.; Mattern, Michael R.; Johnson, Randall K.; Kingston, David G. I.  
 CORPORATE SOURCE: Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061-0212, USA  
 SOURCE: Journal of Natural Products (2000), 63(7), 1046  
 CODEN: JNPREF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Compds. 1 and 2 have been previously reported from *Combretum kraussii* by Varotta and colleagues [Pelizzoni, F.; Verotta, L.; Rogers, C. B.; Colombo, R.; Pedrotti, B.; Balconi, G.; Erba, E.; D'Incalci, M. Nat. Prod. Lett. 1993, 1, 273-280], and their synthesis has also been reported [Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. Carbohydr. Res. 1997, 301, 95-109].

IT 109971-63-3P, Combretastatin A-1 156085-79-9P  
 RI: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
 (Isolation of bioactive compds. from *Combretum erythrophyllum* (Erratum))

RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

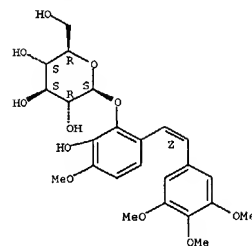
Double bond geometry as shown.



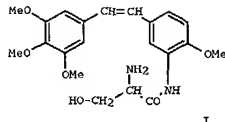
RN 156085-79-9 CAPLUS  
 CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.

L24 ANSWER 79 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

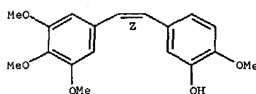


L24 ANSWER 80 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:373651 CAPLUS  
 DOCUMENT NUMBER: 133:129612  
 TITLE: Synthesis and antitumor activities of amino acid prodrugs of amino-combretastatins  
 AUTHOR(S): Ohsumi, Koji; Hatanaka, Toshihiro; Nakagawa, Ryusuke; Fukuda, Yumiko; Morinaga, Yoshihiro; Suga, Yasuyo; Nihei, Yukio; Ohishi, Kazuo; Akiyama, Yukio; Tsuji, Takashi  
 CORPORATE SOURCE: Pharmaceutical Research Laboratories, Ajinomoto Co. Inc., Kawasaki, 210-8681, Japan  
 SOURCE: Anti-Cancer Drug Design (1999), 14(6), S39-S48  
 CODEN: ACDDEA; ISSN: 0266-9536  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB The synthesis and antitumor activity of water-sol. amino acid prodrugs of amino-combretastatins are reported. Among the synthesized compds., AC-7100 (I-HCl) showed enhanced antitumor activity and decreased toxicity in a Colon 26 murine adenocarcinoma model. I showed improved soly. and was easily formulated for in vivo administration. I was cleaved to generate the parent compd., CS-39, in the whole blood of mice as well as man, possibly by the action of amino peptidase on the erythrocyte membrane.  
 IT 117048-59-6, Combretastatin A-4  
 RI: PRP (Properties)  
 (synthesis and antitumor activities of amino acid prodrugs of amino-combretastatins)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 81 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:351266 CAPLUS  
 DOCUMENT NUMBER: 132:345122  
 TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors  
 INVENTOR(S): Huyberechts, Guido; Jordens, Sven  
 PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen  
 SOURCE: Eur. Pat. Appl., 18 pp.  
 CODEN: EPXNDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

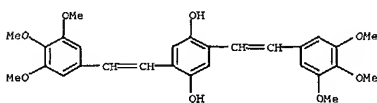
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1999-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117  
 US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT 270069-97-IDP, alkyl deriva.  
 RI: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)

RN 270069-97-1 CAPLUS  
 CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 80 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 82 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:351265 CAPLUS  
 DOCUMENT NUMBER: 132:345121  
 TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors  
 INVENTOR(S): Huyberechts, Guido; Jordens, Sven  
 PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen  
 SOURCE: Eur. Pat. Appl., 14 pp.  
 CODEN: EPXNDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

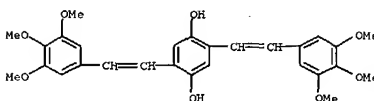
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 2002048751 A1 20020425  
 EP 1998-870254 A 19981117  
 US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT 270069-97-IDP, alkyl deriva.  
 RI: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)

RN 270069-97-1 CAPLUS  
 CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L24 ANSWER 83 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:279432 CAPLUS  
 DOCUMENT NUMBER: 132:171912  
 TITLE: Combination chemotherapy with combretastatin A-4 phosphate and 5-fluorouracil in an experimental murine colon adenocarcinoma  
 AUTHOR(S): Grosios, K.; Loadman, P. M.; Swaine, D. J.; Pettit, G. R.; Bibby, M. C.  
 CORPORATE SOURCE: Clinical Oncology Unit, University of Bradford, Bradford, BD71DE, UK  
 SOURCE: Anticancer Research (2000), 20(1A), 229-233  
 CODEN: ANTRD4 ISSN: 0250-7005  
 PUBLISHER: International Institute of Anticancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

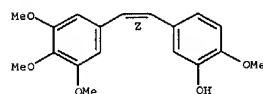
AB The di-sodium phosphate pro-drug of combretastatin A-4 (comba-4P) is undergoing Phase I clin. trial in the USA and UK. Its mechanism of action is thought to be related to tubulin-binding properties that result in rapid, tumor endothelial cell damage, neo-vascular shutdown and subsequent hemorrhagic necrosis. Drugs that work by this mechanism are unlikely to eradicate the tumor as a single agent but should potentiate std. chemotherapy. This study demonstrates that extensive necrosis occurred in a treated refractory murine colon adenocarcinoma but the damage was not accompanied by any measurable effect on tumor growth. Tumors continued to grow from the viable rim that remained. Combination chemotherapy with 5-fluorouracil (5-FU) resulted in significant (p<0.01) antitumor effects. Measurement of 5-FU concns. suggested that this was true synergism and not simply a pharmacokinetic interaction due to the vascular mechanism of comba-4P. The study suggests that if an antivasculature mechanism can be demonstrated in humans, combination chemotherapy should be rapidly assessed in a clin. setting.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination chemotherapy with combretastatin A-4 phosphate and 5-fluorouracil in an exptl. murine colon adenocarcinoma)

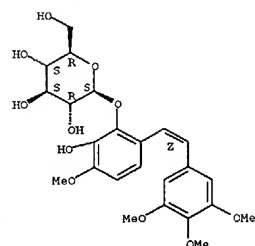
RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 84 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 84 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:173533 CAPLUS  
 DOCUMENT NUMBER: 132:134565  
 TITLE: Bioactive Compounds from Combretum erythrophyllum  
 AUTHOR(S): Schwikard, Sianne; Zhou, Bing-Nan; Glass, Thomas E.; Sharp, Jessica L.; Mattern, Michael R.; Johnson, Randall K.; Kingston, David G. I.  
 CORPORATE SOURCE: Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061-0212, USA  
 SOURCE: Journal of Natural Products (2000), 63(4), 457-460  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

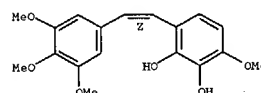
AB A methanol ext. of Combretum erythrophyllum showed inhibitory bioactivities in a yeast-based microtiter assay for DNA-damaging agents. Bioassay-guided fractionation of this ext. yielded two known bioactive compds., combretastatin A-1 and (-)-combretastatin, and two new bioactive glucosides, combretastatin A-1 2'-beta-D-glucoside and combretastatin B-1 2'-beta-D-glucoside. The structures of the new compds. were assigned by 1H and 13C NMR, DEPT, HMQC, and HMBC spectra.

IT 109971-63-3P, Combretastatin A-1 156085-79-9P  
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)

(isolation of bioactive compds. from Combretum erythrophyllum)

RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 156085-79-9 CAPLUS  
 CN beta-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.

L24 ANSWER 85 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:135956 CAPLUS  
 DOCUMENT NUMBER: 132:302959  
 TITLE: Multiple Flexible Alignment with SEAL: A Study of Molecules Acting on the Colchicine Binding Site  
 AUTHOR(S): Feher, Miklos; Schmidt, Jonathan M.  
 CORPORATE SOURCE: Nanodesign Inc., Guelph, ON, N1G 4Y5, Can.  
 SOURCE: Journal of Chemical Information and Computer Sciences (2000), 40(2), 495-502  
 CODEN: JCISDH; ISSN: 0095-2338  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB An extension of the steric and electrostatic alignment alignment (SEAL) method (Multiseal) is described that allows the overlay of multiple mols. and conformations. The method is well-suited for the systematic study of possible alignments, also revealing information about the conformational energies assoc. with a given overlay. It has been tested on three examples: angiotensin II antagonists, 5-HT3 antagonists, and dopaminergic compds. The utility of the method is further demonstrated in an anal. of mols. that putatively bind to the colchicine site of tubulin. On the basis of its overlay with colchicine, allcolchicine, 2-methoxy-5-(2',3',4'-trimethoxyphenyl)tropane, and combretastatin A-4, it appears that 2-methoxyestradiol (2-ME) is unlikely to fit the colchicine site properly. The weak antimitotic activity of 2-ME may be explained by its partial fit in the site.

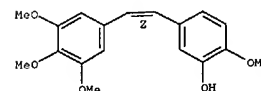
IT 117048-59-6, Combretastatin A-4  
 RL: BFR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(multiple flexible alignment with SEAL in study of mols. acting on colchicine binding site)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 86 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:127298 CAPLUS  
 DOCUMENT NUMBER: 133:68491  
 TITLE: The new tubulin-inhibitor combretastatin A-4 enhances thermal damage in the BT4An rat glioma  
 AUTHOR(S): Eikesdal, H. P.; Schem, B.-C.; Mella, O.; Dahl, O.  
 CORPORATE SOURCE: Haukeland Hospital, Department of Oncology, University of Bergen, Bergen, Norway  
 SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 46(3), 645-652  
 CODEN: IJROPD3; ISSN: 0360-3016  
 PUBLISHER: Elsevier Science Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

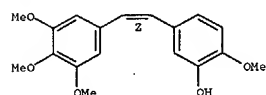
AB The toxicity of combretastatin A-4 disodium phosphate (CA-4) and its vascular effects in the s.c. (s.c.) BT4An rat glioma were investigated, and addnl., the tumor response of CA-4 combined with hyperthermia was detd. For assessment of drug toxicity, rats were given 50, 75, or 100 mg/kg CA-4 and followed by daily registration of wt. and side effects. Interstitial tumor blood flow was detd. by laser Doppler flowmetry in rats injected with 50 mg/kg CA-4. In the tumor response study the authors administered CA-4 50 mg/kg alone or combined with hyperthermia (water bath 44.degree. for 60 min) 0 or 3 h later. The authors found that CA-4, at a well-tolerated dose of 50 mg/kg, induced a considerable time-dependent decrease in the tumor blood flow. Tumor blood flow was reduced by 47-55% during the 1st 110 min after injecting CA-4, and thereafter remained decreased until the measurements were terminated. Administering CA-4 3 h before hyperthermia yielded the best tumor response and increased tumor growth time significantly compared with simultaneous administration of CA-4 and hyperthermia ( $P = 0.03$ ). Interestingly, CA-4 alone did not influence tumor growth. Thus, CA-4 induces a gradual reductn. in tumor blood flow which can be exploited to sensitize the BT4An tumor for hyperthermia.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USBS (Uses)

(combretastatin A-4 combined with hyperthermia enhanced damage in the BT4An glioma)

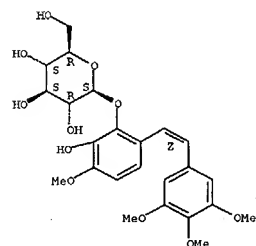
RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 87 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

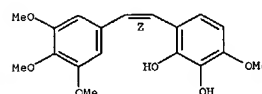
L24 ANSWER 87 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:100968 CAPLUS  
 DOCUMENT NUMBER: 132:234333  
 TITLE: Uterotonic constituents from Combretum kraussii  
 AUTHOR(S): Brookes, K. Bridget; Doudoukina, Olga V.; Katsoulis, Lynn C.; Veale, D. Joy H.  
 CORPORATE SOURCE: Technikon Mangosuthu, Jacobs, 4026, S. Afr.  
 SOURCE: South African Journal of Chemistry (1999), 52(4), 127-132  
 CODEN: SAJCDG; ISSN: 0379-4350  
 PUBLISHER: South African Chemical Institute  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The authors have established that certain exts. of Combretum kraussii Hochst roots cause contractions in isolated rat uterine tissue, and have purified the most active uterotonic components. The mode of action of the various exts./components on isolated rat uterus falls into three different categories. The activity of crude exts. from leaves and branches of C. erythrophyllum (Burch.) Sond. and C. kraussii Hochst was also measured. The following compds. were identified from root exts.: combretastatin, combretastatin A-1 and combretastatin B-1, as well as the corresponding 2-O-beta-D-glucosides of the latter two combretastatins, .beta.-sitosterol, ellagic acid and the di- and tri-Me ethers of ellagic acid. This is the first report of the occurrence of combretastatin and ellagic acid derivs. in this Combretum species.

IT 109971-63-3, Combretastatin A-1 156085-79-9  
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)  
 (uterotonic constituents from Combretum kraussii)

RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 156085-79-9 CAPLUS  
 CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.

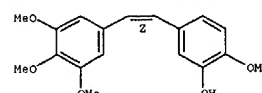
L24 ANSWER 88 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:97483 CAPLUS  
 DOCUMENT NUMBER: 132:260306  
 TITLE: Evaluation of antivasular and antimetabolic effects of tubulin binding agents in solid tumor therapy  
 AUTHOR(S): Nihel, Yukio; Suzuki, Manabu; Okano, Akira; Tsuji, Takashi; Akiyama, Yukio; Tsuruo, Takashi; Saito, Sachiko; Hori, Katsuyoshi; Sato, Yasufumi  
 CORPORATE SOURCE: Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., Kawasaki, 210-8681, Japan  
 SOURCE: Japanese Journal of Cancer Research (1999), 90(12), 1387-1396  
 CODEN: JJCRPF; ISSN: 0910-5050  
 PUBLISHER: Japanese Cancer Association  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Tubulin binding agents (TBAs) reduce tumor perfusion and inhibit mitosis of tumor cells in solid tumors, but it is not clear which effects contribute to the suppression of solid tumor growth. We evaluated the antivasular and antimetabolic effects of several TBAs, combretastatin A-4 (CS A-4) phosphate, AC-7700, a novel CS A-4 deriv., colchicine, E7010, and vinblastine, on s.c. (s.c.) murine colon26 adenocarcinoma (c26). Tolerable doses of vinblastine and E7010 strongly inhibited tumor growth and induced mitotic arrest of tumor cells without affecting tumor perfusion. Colchicine had no effect on tumor growth and perfusion. When the injected dose was increased to the lethal range, however, these drugs markedly reduced tumor perfusion and caused necrosis of tumor tissue. Within the tolerable dose range, AC-7700 both strongly suppressed tumor growth and reduced tumor perfusion, and CS A-4 phosphate also exhibited a moderate antivasular effect. To evaluate the contribution of antivasular activity of TBAs to tumor growth suppression, excluding their direct cytotoxic effect on tumor cells, we established c26/acr, which is resistant to TBAs in vitro. Although E7010 showed a reduced suppressive effect on s.c. c26/acr tumor growth as compared with its effect on wild-type c26, AC-7700 remained potent against both cell lines. These results indicate that TBAs exert antivasular and antimetabolic effects on solid tumors with marked differently ED ranges from agent to agent, and that the antivasular effect of TBAs inhibits solid tumor growth independently of the direct cytotoxic effect on tumor cells.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USBS (Uses)  
 (evaluation of antivasular and antimetabolic effects of tubulin binding agents in solid tumor therapy)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

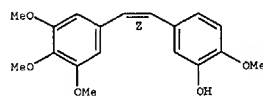
L24 ANSWER 88 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 89 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:56669 CAPLUS  
DOCUMENT NUMBER: 132:303079  
TITLE: In vivo and in vitro evaluation of combretastatin A-4 and its sodium phosphate prodrug  
AUTHOR(S): Grosios, X.; Holwell, S. E.; McGown, A. T.; Pettit, G. R.; Bibby, M. C.  
CORPORATE SOURCE: Clinical Oncology Unit, University of Bradford, Bradford, BD7 1DP, UK  
SOURCE: British Journal of Cancer (1999), 81(8), 1318-1327  
CODEN: BJCAAI; ISSN: 0007-0920  
PUBLISHER: Churchill Livingstone  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The antitumor effects and mechanism of action of combretastatin A-4 and its prodrug, combretastatin A-4 disodium phosphate, were examd. in s.c. and orthotopically transplanted exptl. colon tumors in mice. Addnl., the ability of these compds. to directly interfere with endothelial cell behavior was also examd. in human vein endothelial cell (HUEVC) cultures. Combretastatin A-4 (150 mg/kg, i.p.) and its water-sol. prodrug (100 mg/kg, i.p.) caused almost complete vascular shutdown (after 4 h), extensive hemorrhagic necrosis which started 1 h after treatment and significant tumor growth delay in MAC 15A s.c. colon tumors. Similar vascular effects were obtained in MAC 15 orthotopic tumors and SW620 human colon tumor xenografts treated with the prodrug. More importantly, in the orthotopic models, necrosis was seen in vascularized metastatic deposits but not in avascular secondary deposits. The possible mechanism giving rise to these effects was examd. in HUEVC cells. Here, cellular networks formed in type I calf-skin collagen layers, and these networks were completely disrupted when the layers were incubated with a noncytotoxic concn. of combretastatin A-4 or its prodrug. This effect started after 4 h and was complete by 24 h. The same noncytotoxic concns. resulted in disorganization of F-actin and .beta.-tubulin 1 h after treatment. In conclusion, combretastatin A-4 and its prodrug caused extensive necrosis in MAC 15A s.c. and orthotopic colon cancer and metastases, resulting in antitumor effects. Necrosis was not seen in avascular tumor nodules, suggesting a vascular mechanism of action.

IT 117048-59-6, Combretastatin A4  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(colon cancer inhibition by combretastatin A-4 and its sodium phosphate prodrug)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

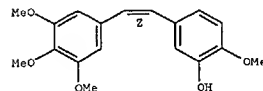
Double bond geometry as shown.



L24 ANSWER 89 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

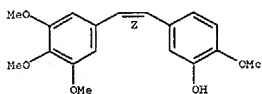
L24 ANSWER 90 OF 157 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 1999:707755 CAPLUS  
DOCUMENT NUMBER: 132:35492  
TITLE: Synthesis and biological evaluation of novel photoaffinity labeling reagents and nitrogen-containing compounds modeled after combretastatin a-4  
AUTHOR(S): Mejia, Maria Del Pilar  
CORPORATE SOURCE: Baylor Univ., Waco, TX, USA  
SOURCE: (1999) 266 pp. Avail.: UMI, Order No. DA9925082  
From: Diss. Abstr. Int., B 1999, 60(5), 2137  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
AB Unavailable  
IT 117048-59-6, Combretastatin a4  
RL: MSC (Miscellaneous)  
(synthesis and biol. evaluation of novel photoaffinity labeling reagents and nitrogen-contg. compds. modeled after combretastatin a4)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

Double bond geometry as shown.



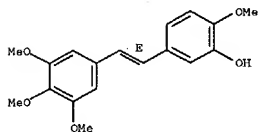
L24 ANSWER 91 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:572221 CAPLUS  
 DOCUMENT NUMBER: 131:336876  
 TITLE: The synthesis of (E)- and (Z)-combretastatins A-4 and a phenanthrene from Combretum cafferum  
 AUTHOR(S): Lawrence, Nicholas J.; Ghani, Fazni Abdul; Hepworth, Lucy A.; Hadfield, John A.; McGown, Alan T.; Pritchard, Robin G.  
 CORPORATE SOURCE: Department Chemistry, UMIST, Manchester, M60 1QD, UK  
 SOURCE: Synthesis (1999), (9), 1656-1660  
 CODEN: SYNTBF; ISSN: 0039-7881  
 PUBLISHER: Georg Thieme Verlag  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 131:336876  
 AB The synthesis of the trans-stilbene (E)-combretastatin A-4 was achieved via a Horner-Wittig reaction of 3,4,5-(MeO)3C6H2CH2P(O)Ph2. The anticancer drug (Z)-combretastatin A-4 was prepd. by the hydroboration/protonation of a diaryl alkyne (no data).  
 IT 117048-59-6P, Combretastatin A-4 117048-62-1P, E-Combretastatin A-4  
 RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of combretastatin A-4 and Combretum phenanthrene)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

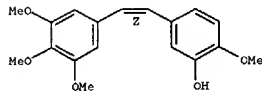
Double bond geometry as shown.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 92 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:567462 CAPLUS  
 DOCUMENT NUMBER: 132:180406  
 TITLE: Synthesis of combretastatin A-4 derivatives, phenstatin, phakellistatin 5, and an approach to dolastatin 17  
 AUTHOR(S): Toki, Brian Eric  
 CORPORATE SOURCE: Arizona State Univ., Tempe, AZ, USA  
 SOURCE: (1999) 369 pp. Avail.: UMI, Order No. DA9924211  
 DOCUMENT TYPE: From Diss. Abstr. Int., B 1999, 60(3), 1093  
 LANGUAGE: Dissertation  
 AR Unavailable  
 IT 117048-59-6P, Combretastatin A-4  
 RL: SPN (Synthetic preparation); PREP (Preparation) (synthesis of combretastatin A-4 deriva., phenstatin, phakellistatin 5, and approach to dolastatin 17)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 91 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 93 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:529049 CAPLUS  
 DOCUMENT NUMBER: 131:175072  
 TITLE: Hydroxylation-activated drug release, and prodrug preparation  
 INVENTOR(S): Potter, Gerard Andrew; Patterson, Lawrence Hylton; Burke, Michael Danny  
 PATENT ASSIGNEE(S): De Montfort University, UK  
 SOURCE: ECT Int. Appl., 53 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

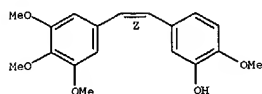
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940944	A2	19990819	WO 1999-GB416	19990210
WO 9940944	A3	19990923		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, A2, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2334256	A1	19990818	GB 1998-2957	19980212
US 2002037296	A1	20020328	US 1998-115016	19980714
CA 2319837	AA	19990819	CA 1999-2319837	19990210
AU 9925315	A1	19990830	AU 1999-25315	19990210
EP 1069915	A2	20010124	EP 1999-905005	19990210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:  
 GB 1998-2957 A 19980212  
 US 1998-115016 A 19980714  
 WO 1999-GB416 W 19990210

OTHER SOURCE(S): MARPAT 131:175072  
 AB The invention concerns prodrugs whose arom. oxidn., particularly their enzymic arom. hydroxylation, results in their activation by the release of a drug moiety. It particularly concerns antitumor prodrugs and those which are specifically activated by the hydroxylation activity of the P 450 enzyme CYP1B1. Also provided are methods of detection of arom. oxidn. activity. Prepn. of prodrugs of the invention is described.  
 IT 117048-59-6  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (biol. hydroxylation activated drug release, and prodrug prepn.)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

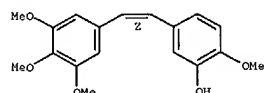
Double bond geometry as shown.

L24 ANSWER 93 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



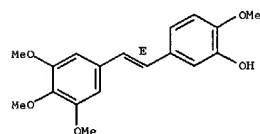
L24 ANSWER 94 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses) (prepn. and formulation of combretastatin A4 prodrugs and their trans-isomers for use as antitumor agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



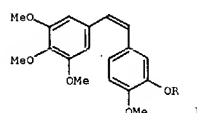
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 94 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:451301 CAPLUS  
 DOCUMENT NUMBER: 131:73507  
 TITLE: Preparation and formulation of combretastatin A4 prodrugs and their trans-isomers for use as antitumor agents  
 INVENTOR(S): Pettit, George R.; Rhodes, Monte R.  
 PATENT ASSIGNEE(S): Arizona State University, USA  
 SOURCE: PCT Int. Appl., 55 pp.  
 CODEN: PIKXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9935150	A1	19990715	WO 1999-US419	19990108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2314238	AA	19990715	CA 1999-2314238	19990108
EP 1045853	A1	20001025	EP 1999-902121	19990108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002500227	T2	20020108	JP 2000-527548	19990108
PRIORITY APPLN. INFO.:			US 1996-71070P	P 19980109
			US 1998-111531P	P 19981209
			WO 1999-US419	W 19990108

GI



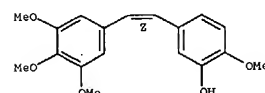
AB Combretastatin A4 I (R = H) and analogous phosphate prodrugs I [R = PO(OR1)OR2; R1, R2 = H, Me, Ca, Cs, Li, Mg, Mn, Zn, indazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, verapamil; R1 = R2 = H, benzyl] and (E)-Combretastatin A4 phosphate analogs were prepd. and formulated for use as water sol. antineoplastic agents. Thus, combretastatin A4 was reacted with dibenzyl phosphite to give dibenzyl ester I [R = P(O)(OCH2CH2)2] in 98% yield. Also, combretastatin A4 was converted to the sodium phosphate salt I [R = PO3HNa] via the formation of the silylethyl ester I [R = P(O)(OCH2CH2SiMe3)2]. The combretastatin A4 phosphate esters were tested for antitumor activity against a variety of cancer cell lines and were also tested for antimicrobial activity against bacterial and fungal strains.  
 IT 117048-59-6, Combretastatin A4 117048-62-1, (E)-Combretastatin A4

L24 ANSWER 95 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:449666 CAPLUS  
 DOCUMENT NUMBER: 132:90067  
 TITLE: Examples of adjuvant treatment enhancing the antitumor effect of photodynamic therapy  
 AUTHOR(S): Korbalik, Miladen; Cecic, Ivana; Sun, Jinghai; Chaplin, David J.  
 CORPORATE SOURCE: British Columbia Cancer Agency, Vancouver, BC, Can.  
 SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1999), 3592(Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy VIII), 65-72  
 CODEN: PSISDG; ISSN: 0277-786X  
 PUBLISHER: SPIE-The International Society for Optical Engineering  
 JOURNAL: General Review  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB A review with 51 refs. Strategies for improving the clin. efficacy of photodynamic therapy (PDT) in treatment of solid cancers include applications of different types of adjuvant treatments in addn. to this modality that may result in superior therapeutic outcome. Examples of such an approach investigated using mouse tumor models are presented in this report. It is shown that the cures of PDT treated s.c. tumors can be substantially improved by adjuvant therapy with: metoclopramide (enhancement of cancer cell apoptosis), combretastatin A4 (selective destruction of tumor neovasculature), Roussin's Black Salt (light activated tumor localized release of nitric oxide), or dendritic cell-based adoptive immunotherapy (immune rejection of treated tumor).  
 IT 117048-59-6, Combretastatin A4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (adjuvant treatment enhancing antitumor effect of photodynamic therapy)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 96 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:297331 CAPLUS  
 DOCUMENT NUMBER: 130:342996  
 TITLE: Heparin-binding growth factor derivatives  
 INVENTOR(S): Gallagher, John Thomas; Fye, David Alexander  
 PATENT ASSIGNEE(S): Cancer Research Campaign Technology Limited, UK  
 SOURCE: PCT Int. Appl., 76 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921588	AI	19990506	WO 1998-GB3201	19981028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TH				
RW: GH, GN, HE, LS, MW, SD, SZ, UG, ZW, AI, EE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SF, SJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9910391	AI	19990517	AU 1999-10391	19981028
PRIORITY APPLN. INFO.:			GB 1997-22604	19971028
			WO 1998-GB3201	19981028

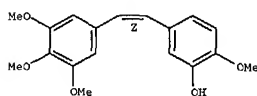
AB Covalently crosslinked conjugates of heparin-binding growth factors and heparin or heparan sulfate (HS) oligosaccharides which can be used as therapeutic agents for modulating the biol. activity of such growth factors and/or for targeted delivery of drugs are disclosed. Such conjugates enable exogenous growth factors to be administered to mammals for medical treatment so as either to promote or to inhibit growth factor biol. activity, or to act as targeting carriers of drug mols. linked thereto. Covalent crosslinked conjugates of HS oligosaccharides and basic fibroblast growth factor were prepd.

IT 117048-59-6D, Combretastatin, derivs.  
 RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
 (heparin-binding growth factor derivs.)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 97 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:284035 CAPLUS  
 DOCUMENT NUMBER: 131:129806  
 TITLE: Antineoplastic agents 393. Synthesis of the trans-isomer of combretastatin A-4 prodrug  
 AUTHOR(S): Pettit, George R.; Rhodes, Monte R.; Herald, Delbert L.; Chaplin, Dai J.; Stratford, Michael R. L.; Hamel, Ernest; Pettit, Robin K.; Chapuis, Jean-Charles; Oliva, Deanna  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2494, USA  
 SOURCE: Anti-Cancer Drug Design (1998), 13(8), 981-993  
 CODEN: ACDDEA; ISSN: 0266-9536  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

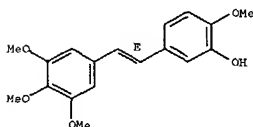
AB The (E)-stilbene isomer (2a) of the (Z)-combretastatin A-4 prodrug (1b) was efficiently prepd. from (E)-combretastatin A-4 by a reaction sequence employing phosphorylation (dibenzyl chlorophosphate), cleavage (trimethylsilylacetate) of the benzyl ester and reaction of the resulting phosphoric acid with sodium methoxide. The sodium phosphate product (2c) was also found to be an important side-product, presumably from iodine-catalyzed isomerization, when the analogous synthetic route was used to obtain the combretastatin A-4 prodrug (1b). The phosphoric acid precursor of prodrug 1b derived from (Z)-combretastatin A-4 (1a) was converted into a series of metal cation and ammonium cation salts to evaluate effects on human cancer cell growth, antimicrobial activities and soly. behavior.

IT 117048-62-1  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis of the antitumor trans-isomer of combretastatin A-4 prodrug)

RN 117048-62-1 CAPLUS

CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

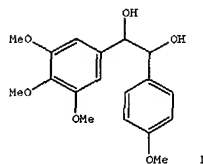
Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 96 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 98 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:282459 CAPLUS  
 DOCUMENT NUMBER: 131:129806  
 TITLE: Design and synthesis of novel antimitotic agents for colchicine binding site of tubulin  
 AUTHOR(S): Nishikawa, A.; Shirai, R.; Onoda, T.; Takahashi, M.; Okabe, T.; Koiso, Y.; Iwasaki, S.  
 CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan  
 SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (1997), 39th, 457-462  
 CODEN: TYKYDS  
 PUBLISHER: Nippon Kagakshi  
 DOCUMENT TYPE: Journal  
 LANGUAGE: Japanese



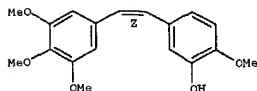
AB Combretastatin A-4 isolated from *Combretum cafferum* is reported to be one of the most potent antimitotic agents which strongly inhibits the polymn. of brain tubulin by binding to the colchicine site (CLC site). Common elements can be found among the structures of the active combretastatins congeners and of other well-known CLC site ligands such as colchicine, etoposide and podophyllotoxin. It has been proposed that CLC site ligands retain optically active conformation at the binding site of tubulin. Although Combretastatin A-4 is not a chiral mol., it is expected to exist as chiral conformer induced by the binding to tubulin. A series of conformationally restricted heterocyclic combretastatin analogs have been synthesized from (R,R)-1, (S,S)-1 and (R,S)-1 and their inhibitory activity of microtubule assembly was evaluated. (4S,5S)-4-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1,3-dioxolane showed moderate antimitotic activity while its enantiomer and other diastereomers synthesized were inactive. Curacin A is a powerful antimitotic agent isolated from an Caribbean cyanobacterium *Lyngbya majuscula* in 1994. Although curacin A binds to CLC site as combretastatin A-4 does, there is no structural similarity to other known CLC site ligands. A variety of side chain analogs of curacin A were synthesized and the effect to in vitro microtubule polymn. was examd. However, compds. synthesized showed weak or no activity suggesting that the side chain was restrictly recognized by microtubule proteins.

IT 117048-59-6, Combretastatin A-4  
 RL: RAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (design and synthesis of novel antimitotic agents for colchicine binding site of tubulin)

RN 117048-59-6 CAPLUS

L24 ANSWER 99 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

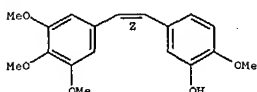
Double bond geometry as shown.



L24 ANSWER 99 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:241795 CAPLUS  
 DOCUMENT NUMBER: 131:39356  
 TITLE: Combretastatin A-4 phosphate as a tumor vascular-targeting agent: early effects in tumors and normal tissues  
 AUTHOR(S): Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J. Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK  
 CORPORATE SOURCE: Cancer Research (1999), 59 (7), 1626-1634  
 SOURCE: CODEN: CNREAS; ISSN: 0008-5472  
 PUBLISHER: AACR Subscription Office  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium combretastatin A-4 3-0-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quant. autoradiog. was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which by 6 h was reduced approx. 100-fold. The spleen was the most affected normal tissue with a 7-fold reduct. in blood flow at 6 h. Calens. of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quant. autoradiog. showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the nitric oxide synthase inhibitor, N.omega.-nitro-L-arginine Me ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue prodn. of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those obsd. in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and combretastatin A-4 (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.  
 IT 117048-59-6, Combretastatin A-4  
 RI: ADV (Adverse effect, including toxicity); RAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (combretastatin A-4 phosphate as a tumor vascular-targeting agent)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

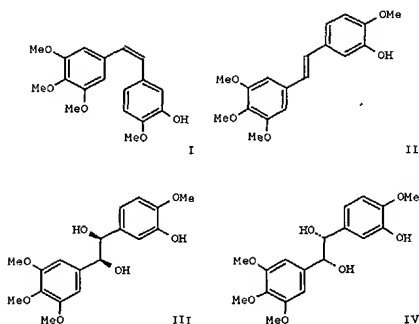
L24 ANSWER 99 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

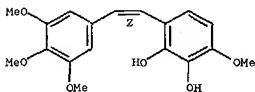
L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:222768 CAPLUS  
 DOCUMENT NUMBER: 131:31823  
 TITLE: Antineoplastic Agents. 410. Asymmetric Hydroxylation of Trans-Combretastatin A-4  
 AUTHOR(S): Pettit, George R.; Toki, Brian E.; Herald, Delbert L.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Chapuis, J. Charles  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Journal of Medicinal Chemistry (1999), 42 (8), 1459-1465  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 131:31823  
 GI



AB The South African willow tree *Combretum caffrum* has yielded a no. of potent cancer cell growth inhibitors. The present SAR studies of the antineoplastic agent combretastatin A-4 (I) were focused mainly on the olefinic bridge to det. the effects on cancer cell growth and, potentially, to better define the combretastatin A-4 binding site on tubulin. The geometric trans-isomer II of combretastatin A-4 was converted to the (1S,2S)- and (1R,2R)-vicinal diols III and IV, resp., under Sharpless' asym. dihydroxylation conditions. Cancer cell line testing showed the (1S,2S)-diol III to be more potent than its enantiomer IV. Diol III weakly inhibited tubulin polymn. (IC50 = 22 .mu.M, vs. 1.2 .mu.M for combretastatin A-4), while IV was inactive (IC50 > 40 .mu.M). Esterification of either stereoisomer at the diol and/or phenolic

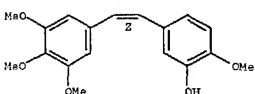
L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 positions resulted in elimination of inhibitory activity.  
 IT 109971-63-3, Combretastatin A-1 117048-59-6,  
 Combretastatin A-4 117048-62-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); BIOL (Biological study)  
 (prepn. of antineoplastic agents via asym. vicinal hydroxylation of  
 trans-Combretastatin A-4)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-  
 (9CI) (CA INDEX NAME)

Double bond geometry as shown.



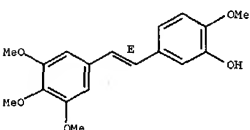
RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

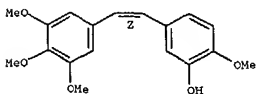
Double bond geometry as shown.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 101 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:129772 CAPLUS  
 DOCUMENT NUMBER: 131:99313  
 TITLE: Positron emission tomography of murine liver  
 metastases and the effects of treatment by  
 combretastatin A-4  
 AUTHOR(S): Zhao, Shai Moore, James V.; Waller, Michael L.;  
 McGown, Alan T.; Hadfield, John A.; Pettit, George R.;  
 Hastings, David L.  
 CORPORATE SOURCE: North West Medical Physics, Christie Hospital (NHS)  
 Trust, Manchester, UK  
 SOURCE: European Journal of Nuclear Medicine (1999), 26(3),  
 231-238  
 CODEN: EJNMB9; ISSN: 0340-6997  
 PUBLISHER: Springer-Verlag  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB There are major potential advantages in non-invasive measurement of  
 preclin. tumor biol. and therapeutic response in clin. relevant, internal  
 body sites, notably the ability to follow outcome in individual animals  
 rather than averaging results from groups. We have exploited positron  
 emission tomog. (PET) to det. the feasibility of detecting liver  
 metastases in B6D2F1 mice using fluorine-18 fluorodeoxyglucose ([18F]FDG)  
 both before and after treatment by the novel cytotoxic agent,  
 combretastatin A-4. The normal distribution of [18F]FDG in the absence of  
 disease was characteristic, with clear delineation of the brain, the heart  
 and the urinary bladder in all studies. In untreated mice with liver  
 metastases, a strong correlation ( $r^2 = 0.98$ ) was found between the quant.  
 ests. of [18F]FDG uptake obtained by anal. of PET images, and those  
 obtained from ex vivo assay of liver plus metastases excised immediately  
 after imaging. In this first series, the effective limit of resoln. was  
 in livers contg. a no. of small metastases (range 8-14) with a single vol.  
 equiv. of approx. 200 mm<sup>3</sup>. PET image anal. was concordant with histol.  
 measurements in showing that single i.p. doses of combretastatin A-4  
 resulted in an av. 30% vol. destruction of metastatic mass by 24 h  
 following administration.  
 IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)  
 ([18F]FDG PET detecting of liver metastases before and after treatment  
 with combretastatin A-4)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.

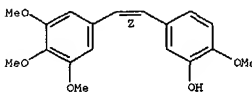


REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 102 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1999:89966 CAPLUS  
 DOCUMENT NUMBER: 130:261394  
 TITLE: Determination of combretastatin A-4 and its drug in  
 plasma by high-performance liquid chromatography  
 AUTHOR(S): Stratford, Michael R. L.; Dennis, Madeleine F.  
 CORPORATE SOURCE: Gray Laboratory Cancer Research Trust, Mount Vernon  
 Hospital, Northwood/Middlesex, HA6 2JR, UK  
 SOURCE: Journal of Chromatography, B: Biomedical Sciences and  
 Applications (1999), 721(1), 77-85  
 CODEN: JCBBER; ISSN: 0378-4347  
 PUBLISHER: Elsevier Science B.V.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB High-performance liq. chromatog. with both absorbance and fluoresce detn.  
 of the potential anti-tumor agent combretastatin A-4 and its phosphate  
 ester in murine and human plasma. The presence of different interfering  
 peaks in the two species makes absorbance detection at 295 nm the method  
 of choice for the mouse, and fluorescence detection (295 nm/390 nm) for  
 human plasma. The calibration was linear over the range studied (0.01-50  
 .mu.M for combretastatin A-4, 0.02-200 .mu.M for combretastatin A-4  
 phosphate), with quantitation limits of 0.05 .mu.M for both drugs in the  
 mouse, and 0.05 .mu.M and 0.0125 .mu.M for the phosphate ester and free  
 drug, resp., in human plasma. The method should be useful for  
 pharmacokinetic studies in the forthcoming Phase 1 clin. trial of  
 combretastatin A-4 phosphate.  
 IT 117048-59-6, Combretastatin A-4  
 RL: ANT (Analyte); ANST (Analytical study)  
 (detn. of combretastatin A-4 and drug in plasma of humans and lab.  
 animals by high-performance liq. chromatog.)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.

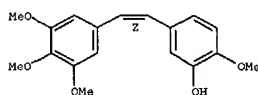


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L24 ANSWER 103 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1998:791632 CAPLUS  
 DOCUMENT NUMBER: 130:138888  
 TITLE: The synthesis of alkenes via epi-phosphonium species:  
 1. An Anti-Wittig elimination  
 AUTHOR(S): Lawrence, Nicholas J.; Muhammad, Faiz  
 CORPORATE SOURCE: Department of Chemistry, University of Manchester  
 Institute of Science and Technology, Manchester, M60  
 100, UK  
 SOURCE: Tetrahedron (1998), 54(50), 15345-15360  
 CODEN: TETRA; ISSN: 0040-4020  
 PUBLISHER: Elsevier Science Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 130:138888  
 AB Anti-1,2-phosphinyl alcs. and their corresponding syn-isomers upon  
 treatment with phosphorus trichloride and triethylamine give E and Z  
 alkenes resp., by an anti elimination. This is in marked contrast to the  
 syn Horner-Wittig elimination of the corresponding 1,2-phosphinoyl alcs.  
 The 1,2-phosphinyl alcs. were prepd. by the redn. of 1,2-phosphinoyl alcs.  
 with cerium(III) chloride/lithium aluminum hydride. The anti elimination  
 is explained by the formation of a transient epi-phosphonium species. An  
 unexpected E-selective Horner-Wittig elimination during the cerium(III)  
 chloride/lithium aluminum hydride redn. of a 1,2-phosphinoyl alc. in which  
 the diphenylphosphinoyl group is adjacent to an aryl group is described.  
 This led to the synthesis of the antimetabolic agent E-combretastatin A-4.  
 An alternative synthesis of the 1,2-phosphinyl alcs. from the  
 corresponding phosphine-borane complex is also described.  
 IT 117048-59-6P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

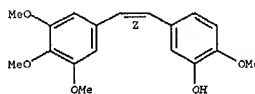
Double bond geometry as shown.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 104 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1998:769241 CAPLUS  
 DOCUMENT NUMBER: 130:95419  
 TITLE: Semiempirical studies of ring twisting in cis-stilbene  
 and related biomolecules  
 AUTHOR(S): Monaco, Regina R.; Gardiner, William C.; Kirschner,  
 Stephen  
 CORPORATE SOURCE: Department of Biology, New York University, New York,  
 NY, 10003, USA  
 SOURCE: International Journal of Quantum Chemistry (1999),  
 71(1), 57-62  
 CODEN: IJQCB2; ISSN: 0020-7608  
 PUBLISHER: John Wiley & Sons, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The geometric and energetic predictions of the MNDO, AM1, and SAM1 models  
 as they describe rotation of the dihedral angle between the plane of one  
 of the Ph rings and the plane of the olefin core of cis-stilbene  
 (cis-1,2-diphenylethylene) were tested for a variety of constraints. All  
 three models predict that distortions away from the stable structure fixed  
 by a compromise between pi-electron and steric repulsions lead to small  
 (at most 1-2 kcal/mol) strain energies and geometry relaxations.  
 Extensive peripheral substitution on the Ph rings present in a prototype  
 natural product having the cis-stilbene structure, Combretastatin A-4  
 (3,4,5-trimethoxy-3'-hydroxy-4'-methoxy-(Z)-stilbene), distorted the  
 shapes of the cis-stilbene barriers to conformation change only minimally.  
 It is concluded that natural products having the cis-stilbene structure  
 should be expected to interact with other biomols. as if the Ph twists are  
 barrier free.  
 IT 117048-59-6, Combretastatin A-4  
 RL: PEP (Physical, engineering or chemical process); PRP (Properties);  
 PHOC (Process)  
 (semiempirical studies of ring twisting in cis-stilbene and related  
 biomols.)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

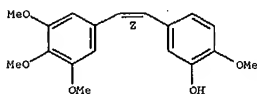
Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 105 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1998:671802 CAPLUS  
 DOCUMENT NUMBER: 130:32771  
 TITLE: Induction of apoptosis in proliferating human  
 endothelial cells by the tumor-specific  
 antiangiogenesis agent combretastatin A-4  
 AUTHOR(S): Iyer, Sudha; Chaplin, Dai J.; Rosenthal, Dean S.;  
 Boulares, A. Hamid; Li, Lu-Yuan; Smulson, Mark E.  
 CORPORATE SOURCE: Department of Biochemistry and Molecular Biology,  
 Georgetown University School of Medicine, Washington,  
 DC, 20007, USA  
 SOURCE: Cancer Research (1998), 58(20), 4510-4514  
 CODEN: CNREAS; ISSN: 0008-5472  
 PUBLISHER: American Association for Cancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The antiangiogenic, tubulin-binding drug combretastatin A-4 exhibits a  
 selective toxicity for proliferating endothelial cells in vitro and  
 induces vascular shutdown in tumor models in vivo. The mechanism of  
 combretastatin A-4 cytotoxicity has now been investigated with cultured  
 proliferating human umbilical vein endothelial cells by examg. various  
 markers of apoptosis. Incubation of cells with 0.1 mM combretastatin A-4  
 induced the conversion (first detected after 6 h) of the CPP32 proenzyme  
 to active caspase-3, a cysteine protease that plays an important role in  
 apoptosis in many cell types; the drug also increased caspase-3 activity.  
 Another early event obsd. was the binding of annexin V to 50% of the cells  
 8 h after drug treatment. Internucleosomal DNA fragmentation, another  
 hallmark of apoptosis, was detected in cells incubated with 0.1 mM  
 combretastatin A-4 for 24 h. Staining with Hoechst 33258 revealed that  
 about 75% of cells exhibited a nuclear morphol. characteristic of  
 apoptosis after incubation with drug for 24 h. Incubation of cells for up  
 to 8 h with combretastatin A-4 did not induce the release of lactate  
 dehydrogenase or increase the uptake of propidium iodide, both indicators  
 of membrane integrity. These results indicate that the selective  
 cytotoxic effect of combretastatin A-4 is mediated by the induction of  
 apoptosis rather than by necrosis and may provide an enhanced clin.  
 strategy in cancer chemotherapy with this new agent.  
 IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
 (Uses)  
 (induction of apoptosis in proliferating human endothelial cells by the  
 tumor-specific antiangiogenesis agent combretastatin A-4)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA  
 INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 105 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

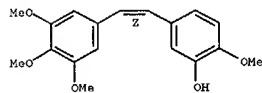
L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:612092 CAPLUS  
 DOCUMENT NUMBER: 129:245037  
 TITLE: Benzo[b]thiophene derivatives, analogs, and combretastatin nitrogen derivatives, useful as anti-mitotic agents which inhibit tubulin polymerization, and as antitumor agents  
 INVENTOR(S): Pinney, Kevin G.; Pettit, George R.; Mocharla, Vani P.; Del, Pilar Majia Maria; Shirali, Anupama  
 PATENT ASSIGNEE(S): Baylor University, USA; Arizona Disease Control Research Commission; Del Pilar Majia, Maria  
 SOURCE: PCT Int. Appl., 85 pp.  
 CODEN: PIXX22  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9839323	A1	19980911	WO 1998-US4380	19980306
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5886025	A	19990323	US 1997-813018	19970306
AU 9866886	A1	19980922	AU 1998-66886	19980306
AU 732917	B2	20010503		
EP 984954	A1	20000315	EP 1998-908991	19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NZ 337866	A	20010629	NZ 1998-337866	19980306
JP 2001527533	T2	20011225	JP 1998-538834	19980306
MX 9908166	A	20000831	MX 1999-8166	19990906
US 6162930	A	20001219	US 1999-380429	19991203
US 2001034454	A1	20011025	US 2000-798394	20001215
PRIORITY APPL. INFO.:			US 1997-813018	A 19970306
			WO 1998-US4380	W 19980306
			US 1999-380429	A1 19991203

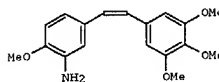
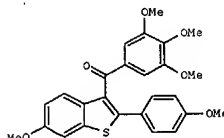
GI

L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 2  
 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



AB Methoxy- and ethoxy-substituted 3-aryl-2-arylbenzo[b]thiophenes and benzo[b]thiophene analogs are described. The compds. are useful for inhibiting tubulin polym., and thus for treating both tumors and infections with flagellated protozoa. Also described are certain diaryl ether benzo[b]thiophene derivs., as well as some analogs derived from dihydronaphthalene, which have proven particularly effective. Certain new benzofuran analogs are further described, as well as certain sulfur oxide benzo[b]thiophene analogs. Important compds. described herein also include the first nitrogen-contg. derivs. of combretastatin. These include nitro, amino and azido combretastatin derivs. For instance, acylation of 2-(4-methoxyphenyl)-6-methoxybenzo[b]thiophene by 3,4,5-trimethoxybenzoyl chloride and AlCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave 63% title compd. I. The IC<sub>50</sub> of I for inhibiting tubulin polym. in vitro was 1.5-2.5 .mu.M, while that for inhibiting growth of 6 human cancer cell lines was 0.049-0.48 .mu.g/ml. Against a different selection of 6 cancer cell lines, the amino combretastatin deriv. II gave even greater growth inhibitions, with IC<sub>50</sub> values of 0.0013 .mu.g/ml or less.

IT 117048-59-69, Combretastatin  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of benzothiophenes and analogs as tubulin polymn. inhibitors and antitumor agents)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 107 OF 157 CAPLUS COPYRIGHT 2003 ACS

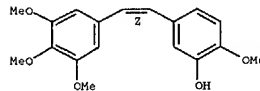
ACCESSION NUMBER: 1998:496731 CAPLUS  
 DOCUMENT NUMBER: 129:211245  
 TITLE: Antimitotic activity of diaryl compounds with structural features resembling combretastatin A-4  
 AUTHOR(S): Aleksandrak, Krzysztof; McGown, Alan T.; Hadfield, John A.  
 CORPORATE SOURCE: Cancer Research Campaign Section Drug Development Imaging, Paterson Institute Cancer Research, Christie Hospital NHS Trust, Manchester, M20 4BX, UK  
 SOURCE: Anti-Cancer Drugs (1998), 9(6), 545-550  
 CODEN: ANTDEW; ISSN: 0959-4973  
 PUBLISHER: Lippincott-Raven Publishers  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Series of diaryl ethers, amines and amides have been synthesized and tested for antitumor activity. These diaryl compds. possess some of the structural features of combretastatin A-4 (a potent antimitotic agent). They were designed to discover whether transferring these structural motifs from stilbenes to heterosubstituted diaryl compds. would enhance their biochem. activities. Mol. modeling studies suggested that these diaryl compds. could adopt conformations similar to combretastatin A-4. However, although some agents were cytotoxic and others could interact with tubulin, none were as potent as combretastatin A-4.

IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antimitotic activity of diaryl compds. with structural features resembling combretastatin A-4)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

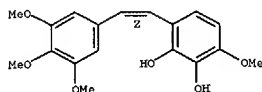


IT 109971-63-3  
 RL: PRE (Properties)  
 (antimitotic activity of diaryl compds. with structural features resembling combretastatin A-4)

RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

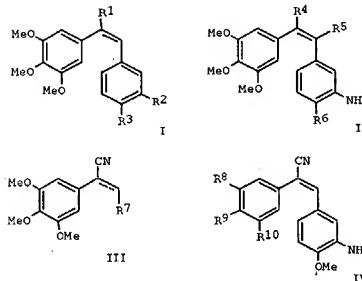
L24 ANSWER 107 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 108 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:450903 CAPLUS  
DOCUMENT NUMBER: 129:202789  
TITLE: Novel Combretastatin Analogs Effective against Murine Solid Tumors: Design and Structure-Activity Relationships  
AUTHOR(S): Ohsumi, Koji; Nakagawa, Ryusuke; Fukuda, Yumiko; Hatanaka, Toshihiro; Morinaga, Yoshihiro; Mihei, Yukio; Ohishi, Kazuo; Suga, Yasuyo; Akiyama, Yukio; Tsuji, Takashi  
CORPORATE SOURCE: Central Research Laboratories, Ajinomoto Company Ltd., Kawasaki, 210 JAPAN, Japan  
SOURCE: Journal of Medicinal Chemistry (1998), 41(16), 3022-3032  
CODEN: JMCMAR; ISSN: 0022-2623  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



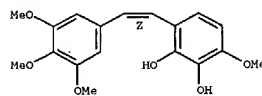
AB A series of combretastatin A-4 (CA-4) analogs, I (R1 = CH<sub>2</sub>OH, CH<sub>2</sub>NH<sub>2</sub>, NH<sub>2</sub>N+Me<sub>3</sub>I<sup>-</sup>, CHO, CN, R2 = H, R3 = OMe; R1 = CN, R2 = NO<sub>2</sub>, OH, NH<sub>2</sub>, R3 = OMe; R1 = CN, R2 = NH<sub>2</sub>, R3 = Me, Cl; R1 = CN, R2 = NHAc, R3 = OMe), II (R4 = H, R5 = CONH<sub>2</sub>, CN, H, R6 = OMe; R4 = CONH<sub>2</sub>, CN, R5 = H, R6 = OMe; R4 = R5 = H, R6 = Me, Cl), III (dashed line = double bond, R7 = C<sub>6</sub>H<sub>4</sub>OMe-4, C<sub>6</sub>H<sub>4</sub>OMe-4-NO<sub>2</sub>-3, C<sub>6</sub>H<sub>4</sub>OMe-4-NH<sub>2</sub>-3, C<sub>6</sub>H<sub>4</sub>OMe-4-NH<sub>2</sub>-3, 2-methoxy-5-pyridyl; dashed line = single bond, R7 = C<sub>6</sub>H<sub>4</sub>OMe-4, C<sub>6</sub>H<sub>4</sub>OMe-4-NO<sub>2</sub>-3, C<sub>6</sub>H<sub>4</sub>OMe-4-NH<sub>2</sub>-3, 2-methoxy-5-pyridyl) and IV (R8 = R9 = R10 = H, OMe; R8 = R10 = H, R9 = OMe; R8 = R9 = OMe, R10 = H), were synthesized, and their cytotoxic effects against murine Colon 26 adenocarcinoma and inhibitory activity on tubulin polym. were evaluated. Since CA-4 has limited aq. soly., the target compds. were designed to improve soly. by introduction

L24 ANSWER 109 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

of a nitrogen-contg. group. Among the compds. synthesized, those with an amino moiety in place of the phenolic OH of CA-4 showed potent antitubulin activity and cytotoxicity against murine Colon 26 adenocarcinoma in vitro. Some of the compds. which were potent in vitro were evaluated in the murine tumor model Colon 26 in vivo. Among these, I.cntdot.HCl (R1 = CN, R2 = NH<sub>2</sub>, R3 = OMe), and II.cntdot.HCl (R4 = R5 = H, R6 = OMe, Me) showed significant antitumor activity in the animal model, while CA-4 was ineffective. I.cntdot.HCl (R1 = CN, R2 = NH<sub>2</sub>, R3 = OMe), and II.cntdot.HCl (R4 = R5 = H, R6 = OMe) were further evaluated in two murine tumor models (Colon 38 and 3LL) and human xenografts HCT-15. These compds. showed potent antitumor activity comparable or superior to that of CDDP. The structure-activity relationships of this series of compds. are also discussed.

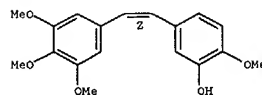
IT 109971-63-3DP, Combretastatin A-1, analogs 117048-59-6DP, Combretastatin A-4, analogs  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn. and antitumor structure-activity relationships of combretastatin analogs)  
RN 109971-63-3 CAPLUS  
CN 1,2-Benzenediol, 3-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

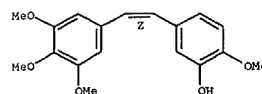
L24 ANSWER 109 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:404526 CAPLUS  
DOCUMENT NUMBER: 129:172497  
TITLE: Magnetic resonance imaging and spectroscopy of combretastatin A4 prodrug-induced disruption of tumor perfusion and energetic status  
AUTHOR(S): Beauregard, D. A.; Thelwall, P. E.; Chaplin, D. J.; Hill, S. A.; Adams, G. E.; Brindle, K. M.  
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1GA, UK  
SOURCE: British Journal of Cancer (1998), 77(11), 1761-1767  
CODEN: BJCAAL; ISSN: 0007-0920  
PUBLISHER: Churchill Livingstone  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The effects of combretastatin A4 prodrug on perfusion and the levels of 31P metabolites in an implanted murine tumor were investigated for 3 h after drug treatment using NMR imaging (MRI) and spectroscopy (MRS). The area of regions of low signal intensity in spin-echo images of tumors increased slightly after treatment with the drug. These regions of low signal intensity corresponded to necrosis seen in histol. sections, whereas the expanding regions surrounding them corresponded to hemorrhage. Tumor perfusion was assessed before and 160 min after drug treatment using dynamic MRI measurements of gadolinium diethylenetriaminepentaacetate (Gd DTPA) uptake and washout. Perfusion decreased significantly in central regions of the tumor after treatment. This was attributed to disruption of the vasculature and was consistent with the hemorrhage seen in histol. sections. The mean apparent diffusion coeff. of water within the tumor did not change, indicating that there was no expansion of necrotic regions during the 3 h after drug treatment. Localized 31P-MRS showed that there was decline in cellular energy status in the tumor after treatment with the drug. The concns. of nucleoside triphosphates within the tumor fell, the inorg. phosphate concn. increased and there was a significant decrease in tumor pH for 80 min after drug treatment. The rapid, selective and extensive damage caused to these tumors by combretastatin A4 prodrug has highlighted the potential of the agent as a novel cancer chemotherapeutic agent. We have shown that the response of tumors to treatment with the drug may be monitored non-invasively using MRI and MRS expts. that are appropriate for use in a clin. setting.

IT 117048-59-6, Combretastatin A4  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(magnetic resonance imaging and spectroscopy of combretastatin A4 prodrug-induced disruption of tumor perfusion and energetic status)  
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

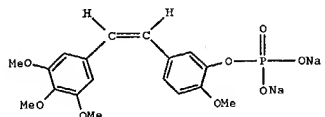


REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 109 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 110 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:301433 CAPLUS  
 DOCUMENT NUMBER: 129:136213  
 TITLE: Antineoplastic agents. 389. New syntheses of the combretastatin A-4 prodrug  
 AUTHOR(S): Pettit, George R.; Rhodes, Monte R.  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA  
 SOURCE: Anti-Cancer Drug Design (1998), 13(3), 183-191  
 CODEN: ACDDDE; ISSN: 0266-9536  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



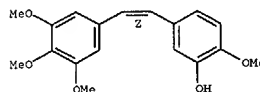
AB Combretastatin A-4 as the phosphate ester prodrug I is a potent antineoplastic and antiangiogenesis substance and is in advanced preclin. development. For the purpose of improving the phosphorylation synthetic sequence from combretastatin A-4, new routes were studied. The phosphorylation step is considerably improved using in situ-generated dibenzyl chlorophosphite. Cleavage of the benzyl esters employing a trimethylchlorosilane/Kal procedure, followed by treatment with Na methoxide, led to the water-sol. prodrug I in high yield.

IT 117048-59-6  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (prepn. of combretastatin A-4 prodrug)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

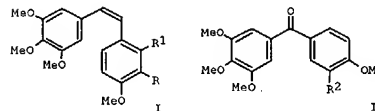


REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 110 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 111 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:253141 CAPLUS  
 DOCUMENT NUMBER: 128:230173  
 TITLE: Antineoplastic Agents. 379. Synthesis of Phenstatin Phosphate  
 AUTHOR(S): Pettit, George R.; Toki, Brian; Herald, Delbert L.; Verdier-Finard, Pascal; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA  
 SOURCE: Journal of Medicinal Chemistry (1998), 41(10), 1688-1695  
 CODEN: JMCHAM; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) antineoplastic constituent combretastatin A-4 (I; R = OH, R1 = H) directed at maintaining the (Z)-stilbene relationship of the olefin di-Ph substituents led to synthesis of a potent cancer cell growth inhibitor designated phenstatin (II; R2 = OH). Initially phenstatin silyl ether (II; R2 = OSiMe2CMe3) was unexpectedly obtained by Jacobsen oxidn. of combretastatin A-4 silyl ether (I; R = OSiMe2CMe2, R1 = H), and the parent phenstatin (II; R2 = OH) was later synthesized in quantity. Phenstatin was converted to the sodium phosphate prodrug (II; R2 = OP(O)(ONa)2) by a dibenzyl phosphite phosphorylation and subsequent hydrogenolysis sequence. Phenstatin (II; R2 = OH) inhibited growth of the pathogenic bacterium Neisseria gonorrhoeae and was a potent inhibitor of tubulin polymn. and the binding of colchicine to tubulin comparable to combretastatin A-4 (I; R = OH, R1 = H). Interestingly, the prodrugs were found to have reduced activity in these biochem. assays. While no significant tubulin activity was obsd. with the phosphorylated deriv. of combretastatin A-4 (I; R = OH, R1 = H), phosphate II (R2 = OP(O)(ONa)2) retained detectable inhibitory effects in both assays.

IT 117048-59-6DP, Combretastatin A-4, analogs and prodrugs  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

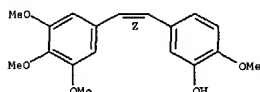
(structure-activity relationship of the antineoplastic agent combretastatin A-4)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 111 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 112 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:232843 CAPLUS

DOCUMENT NUMBER: 128:316915

TITLE: Using a canonical matching to measure the similarity between molecules: the taxol and the combretastatin A1 case

AUTHOR(S): Sello, Guido; Termini, Manuela  
CORPORATE SOURCE: Department of Organic and Industrial Chemistry, University of Milano, Milan, Italy

SOURCE: Advances in Molecular Similarity (1996), 1, 243-266

CODEN: AMOSFB

PUBLISHER: JAI Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The incomplete understanding of tumor proliferation and the structural complexity of the few natural antitumor agents are impediments to the prodn. of effective synthetic drugs. Polyhydroxyphenol derivs. with stilbenic skeleton, such as some combretastatin A1 derivs., proved to be promising as potential antitumor agents. The possibility of modeling structure and biol. activity relationships could allow us to find new drugs to be synthesized more easily and with controlled pharmacol. properties, such as activity and selectivity, thus giving great benefits. Knowing the structure and the properties of one of the few antitumor drugs currently available (taxol) and having at our disposal an anal. method to detect similarities, we started a conformational study of the similarity between taxol and some combretastatin A1 derivs. The aim was to check the possibility of these simple compds. to substitute taxol for its biol. activity. The results obtained have been compared to those from a modeling program (CHEMX) to test and confirm the correctness of our methodol.

IT 109971-63-3, Combretastatin A1

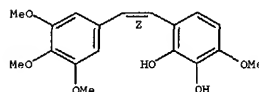
RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(using a canonical matching to measure the similarity between mol. in antitumor drug design)

RN 109971-63-3 CAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 113 OF 157 CAPLUS COPYRIGHT 2003 ACS

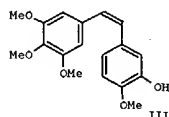
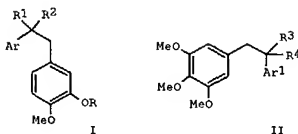
ACCESSION NUMBER: 1998:222502 CAPLUS

DOCUMENT NUMBER: 128:294632

TITLE: Synthesis and antineoplastic activity of combretastatin analogs: heterocombretastatins  
Medarde, Manuel; Ramos, Angel; Caballero, Esther; Pelaez-Lamame de Clairac, Rafael; Lopez, Jose Luis; Gravalos, Dolores Garcia; San Feliciano, Arturo  
CORPORATE SOURCE: Departamento de Quimica Farmaceutica, Facultad de Farmacia, Salamanca, E-37007, Spain  
SOURCE: European Journal of Medicinal Chemistry (1998), 33(1), 71-77

CODEN: EJMCA5; ISSN: 0223-5234  
Editions Scientifiques et Medicales Elsevier  
PUBLISHER: Journal  
DOCUMENT TYPE: Journal  
LANGUAGE: English

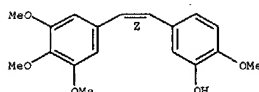
GI



L24 ANSWER 113 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

INDEX NAME

Double bond geometry as shown.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

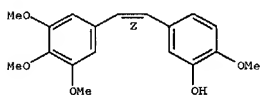
AB Furan and indole analogs I (Ar = 2-furyl, R = H, R1R2 = O; Ar = 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R = R1 = R2 = H; Ar = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R = CH2Ph, R1R2 = SCH2CH2CH2S) and II (Ar1 = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R3 = R4 = H; Ar1 = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R3R4 = O, SCH2CH2CH2S; Ar1 = 2-furyl, 3-furyl, R3 = OH, R4 = H) of combretastatin A-4 (III) were prepd. and assayed for antineoplastic activity. II (Ar1 = 1-methylindol-3-yl, R1R2 = O) showed the best activity (IC50 = 0.6 .mu.M vs. P-388, A-549, HT-29 cells; IC50 = 0.3 vs. MEL-28 cells).

IT 117048-59-6DP, Combretastatin A-4, furan and indole analogs  
RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(synthesis and antineoplastic activity of furan and indole analogs of combretastatin)

RN 117048-59-6 CAPLUS

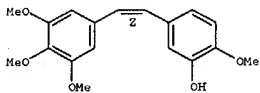
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA

L24 ANSWER 114 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1998:212786 CAPLUS  
 DOCUMENT NUMBER: 128:292670  
 TITLE: Microtubule depolymerization in *Uromyces appendiculatus* by three new antineoplastic drugs: combretastatin A-4, dolastatin 10 and halichondrin B  
 AUTHOR(S): Roberson, Robert W.; Tucker, Bruce; Pettit, George R.  
 CORPORATE SOURCE: Department of Botany, Arizona State University, Tempe, AZ, 85287-1601, USA  
 SOURCE: Mycological Research (1998), 102(3), 378-382  
 CODEN: MYCRER; ISSN: 0953-7562  
 PUBLISHER: Cambridge University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Three new antineoplastic natural products, combretastatin A-4, dolastatin 10 and halichondrin B, have been evaluated for their antimicrotubule activity in *Uromyces appendiculatus* urediniospore germlings using indirect immunofluorescence microscopy. In control germlings microtubules were abundant and mostly oriented parallel to the longitudinal axis of the cell. The microtubule cytoskeleton of germlings treated with 1.3 .times. 10<sup>-5</sup> M (10 .mu.g ml<sup>-1</sup>) dolastatin 10 and 4.5 .times. 10<sup>-5</sup> M (50 .mu.g ml<sup>-1</sup>) halichondrin B disrupted the microtubule cytoskeleton resulting in the near elimination of microtubule-associated fluorescence. Combretastatin A-4 was less effective, requiring a concn. of 3.2 .times. 10<sup>-3</sup> M (1.0 mg ml<sup>-1</sup>) to disrupt the microtubule cytoskeleton. These EDs are consistent with previously examd. antimicrotubule agents (e.g. nocodazole, griseofulvin, vincristine sulfate, and demecolcine).  
 IT 117048-59-6, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (microtubule depolym. in *Uromyces appendiculatus* by three new antineoplastic drugs: combretastatin A-4, dolastatin 10 and halichondrin B)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

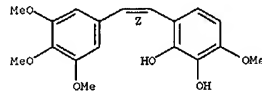


REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 115 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

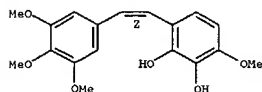


L24 ANSWER 115 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1997:720292 CAPLUS  
 DOCUMENT NUMBER: 127:302918  
 TITLE: Isolation, Synthesis, and Antiplatelet Aggregation Activity of Resveratrol 3-O-.beta.-D-glucopyranoside and Related Compounds  
 AUTHOR(S): Orsini, Fulvia; Verotta, Luisella; Aburjai, Talal; Rogers, Colin B.  
 CORPORATE SOURCE: Centro di Studio per le Sostanze Organiche Naturali, CNR, Milan, 20133, Italy  
 SOURCE: Journal of Natural Products (1997), 60(11), 1082-1087  
 CODEN: JNPRDF; ISSN: 0163-3864  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Resveratrol 3-O-.beta.-D-glucopyranoside (I) has been isolated from the seeds of *Erythrophleum lasianthum* (Caesalpinioidae, Leguminosae), a South African plant used in traditional medicine, and has shown antiplatelet aggregation activity. The synthesis of I, related hydroxystilbenes, and their glucosides has been undertaken to provide larger quantities, for further biol. evaluation, and has been accomplished via Wittig reactions followed by glucosylation under phase transfer catalysis.  
 IT 109971-63-3 117048-59-6  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (resveratrol O-.beta.-D-glucopyranoside isolation, synthesis, and antiplatelet aggregation activity of resveratrol 3-O-.beta.-D-glucopyranoside and related compds.)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.



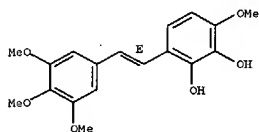
RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1997:452036 CAPLUS  
 DOCUMENT NUMBER: 127:121925  
 TITLE: Synthesis of biologically active polyphenolic glycosides (combretastatin and resveratrol series)  
 AUTHOR(S): Orsini, Fulvia; Pelizzoni, Francesca; Bellini, Barbara; Migliorini, Giuliana  
 CORPORATE SOURCE: Dipartimento di Chimica Organica e Industriale, Centro di Studio per le Sostanze Organiche Naturali del CNR, Milan, 20133, Italy  
 SOURCE: Carbohydrate Research (1997), 301(3-4), 95-109  
 CODEN: CRBRAT; ISSN: 0008-6215  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB (E)-3-(.beta.-D-glucopyranosyloxy)-4',5'-dihydroxystilbene (resveratrol 3-.beta.-D-glucoside, piceid), (Z)-2',3'-dihydroxy-3,4,4',5'-tetramethoxystilbene (combretastatin A-1), (Z)-3'-hydroxy-3,4,4',5'-tetramethoxystilbene (combretastatin A-4), (Z)-2'-hydroxy-3,4,4',5'-tetramethoxystilbene (combretastatin iso-A-4), .alpha.-.beta.-dihydro-2',3'-dihydroxy-3,4,4',5'-tetramethoxystilbene (combretastatin B-1), the corresponding glucosides, and related compds. have been synthesized via Wittig reactions followed by glucosylation under phase-transfer catalysis. Most of the compds. synthesized have been tested with respect to biol. activity (cytostatic, cytotoxic, antimitotic, neurotoxic, antiplatelet aggregation activity).  
 IT 109971-63-3P 109984-84-1P 117048-59-6P  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. of biol. active polyphenolic glycosides)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.



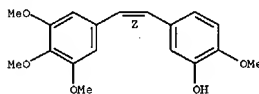
RN 109984-84-1 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
 Double bond geometry as shown.

L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

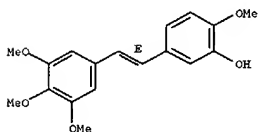
Double bond geometry as shown.



IT 117048-62-1P 156085-79-9P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREF (Preparation)  
(prepn. of biol. active polyphenolic glycosides)

RN 117048-62-1 CAPLUS  
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 156085-79-9 CAPLUS  
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L24 ANSWER 117 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:335437 CAPLUS

DOCUMENT NUMBER: 127:60262

TITLE:

COMBRETASTATIN A-4, an agent that displays potent and selective toxicity toward tumor vasculature  
Dark, Graham G.; Hill, Sally A.; Priese, Vivien E.; Tozer, Gillian M.; Pettit, George R.; Chaplin, Dai J.  
Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SOURCE: Cancer Research (1997), 57(10), 1829-1834

CODEN: CANRES; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

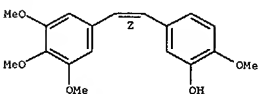
AB Selective induction of vascular damage within tumors represents an emerging approach to cancer treatment. Histol. studies have shown that several tubulin-binding agents can induce vascular damage within tumors but only at doses approximating the max. tolerated dose, which has limited their clin. applicability. In this study, we show that the combretastatin A-4 prodrug induces vascular shutdown within tumors at doses less than one-tenth of the max. tolerated dose. In vitro studies indicate that a short drug exposure results in profound long-term antiproliferative/cytotoxic effects against proliferating endothelial cells but not cells that are quiescent prior to and during drug exposure. Vascular shutdown, within expl. and human breast cancer models in vivo following systemic drug administration, was demonstrated with a redn. in functional vascular vol. of 93% at 6 h following drug administration and persisted over the next 12 h, with corresponding histol. consistent with hemorrhagic necrosis resulting from vascular damage. The actions against tumor vasculature and the broad therapeutic window demonstrate the clin. potential of these drugs and warrant further study to elucidate the mechanisms responsible for the antivascular effects of combretastatin A-4.

IT 117048-59-6, Combretastatin A-4  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combretastatin A-4 in toxicity toward tumor vasculature)

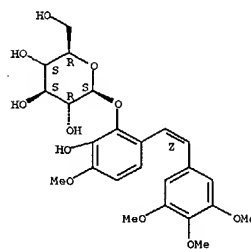
RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

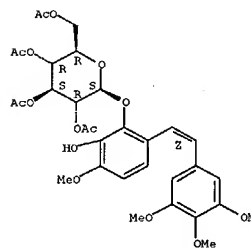
Double bond geometry as shown.



IT 192711-05-0P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREF (Preparation); RACT (Reactant or reagent)  
(prepn. of biol. active polyphenolic glycosides)

RN 192711-05-0 CAPLUS  
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl, 2,3,4,6-tetraacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).  
Double bond geometry as shown.



L24 ANSWER 118 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:328692 CAPLUS

DOCUMENT NUMBER: 127:28629

TITLE:

Synthesis and biological evaluation of 1,1-dichloro-2,3-diarylcyclopropanes as antitubulin and anti-breast cancer agents  
Jonasagadda, Sastry S.; Ter Haar, Ernst; Hamel, Ernest; Lin, Chii M.; Magarian, Robert A.; Day, Billy W.

CORPORATE SOURCE: Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA, 15238, USA

BIOORGANIC &amp; MEDICINAL CHEMISTRY (1997), 5(4), 715-722

CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

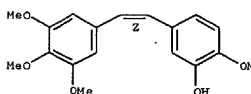
LANGUAGE: English

AB 2-1,1-Dichloro-2,3-diphenylcyclopropane (1) is an effective anti-breast cancer agent in rodents and in cell culture. We recently detd. that 1 inhibits tubulin assembly in vitro and causes microtubule loss in breast cancer cells, leading to accumulation in the G2/M portion of the cell cycle. Aryl ring-halogenated, methoxylated and benzyloxylated derivs. of 1, as well as its E-isomer and the dichlorocyclopropyl deriv. of diethylstilbestrol (DES), were synthesized and tested for their ability to inhibit the assembly of tubulin into microtubules. Including 1, 17 cyclopropyl compds. were tested. One (Z-1,1-dichloro-2-(4-methoxyphenyl)-3-phenylcyclopropane) was found to be more active than 1. In addn., E-1,1-dichlorocyclopropylDES was more potent than DES. The E-isomer of 1 was inactive. The cytostatic activities of the compds. against MCF-7 and MDA-MB231 human breast cancer cells, and their abilities to perturb microtubules in MCF-7 cells were also evaluated. 2-Dichloro-2-(4-fluorophenyl)-3-phenylcyclopropane, Z-1,1-dichloro-2-(4-fluorophenyl)-3-(4-methoxyphenyl)cyclopropane, and Z-1,1-dichloro-2-(4-methoxyphenyl)-3-phenylcyclopropane were more potent than 1 against the breast cancer cells.

IT 117048-59-6, Combretastatin A-4  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(synthesis and biol. evaluation of 1,1-dichloro-2,3-diarylcyclopropanes as antitubulin and anti-breast cancer agents)

RN 117048-59-6 CAPLUS  
CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 119 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1997:198361 CAPLUS  
 DOCUMENT NUMBER: 126:258604  
 TITLE: Effects of novel and conventional anti-cancer agents on human endothelial permeability: influence of tumor secreted factors  
 AUTHOR(S): Watts, Margaret E.; Woodcock, Michael; Arnold, Stephanie; Chaplin, David J.  
 CORPORATE SOURCE: Tumor Microcirculation Group, Gray Lab. Cancer Res. Trust, Middlessex, HA6 2JR, UK  
 SOURCE: Anticancer Research (1997), 17(1A), 71-75  
 CODEN: ANTRD4; ISSN: 0250-7005  
 PUBLISHER: Anticancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB A no. of anti-cancer agents have been implicated in vascular toxicity. The effects have been attributed to direct drug toxicity towards endothelium. Little attention has been focused on the interaction between anticancer drugs, endothelial cells and tumor secreted factors. It is well known that tumors can secrete factors such as vascular permeability factor which do affect endothelial cells and could alter their response to the vascular effects of anticancer drugs. In the present study, we have examined, in vitro, the direct effects of vinblastine (VEL), 5-fluorouracil (5-FU), melphalan (L-PAM) and the novel tubulin inhibitor combretastatin A-1 (CBS) on endothelial permeability under normal and tumor simulated conditions. Monolayers of human umbilical vein endothelial cells (HUVEC) grown on membrane filters were incubated by the human melanoma cell line, RMH-7951 (TCM). VBL caused rapid increase in permeability during the first 20 mins, which was maintained for the duration of the expt. (120 mins). The effect was not altered by TCM or restored to control levels when VBL was replaced by drug-free medium. Similarly, CBS caused a rapid increase in permeability; however, in contrast to VBL, this increase was enhanced by TCM. The changes induced by VBL and CBS were accompanied by contraction of the endothelial F-actin cytoskeleton. Neither L-PAM nor 5-FU altered the permeability of HUVEC monolayers. This study demonstrates that certain anti-cancer agents have a direct effect on endothelial cells, leading to an increase in the permeability of endothelial monolayers. Both VBL and CBS have vascular components in their mode of action which may lead to vascular collapse and tumor necrosis.

IT 109971-63-3, Combretastatin A-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (Novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

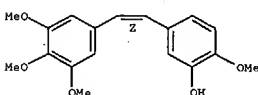
L24 ANSWER 120 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:743457 CAPLUS  
 DOCUMENT NUMBER: 126:89204  
 TITLE: Ethynylation of aryl halides by a modified Suzuki reaction. Application to the syntheses of combretastatin A-4, A-5, and lunularic acid  
 AUTHOR(S): Puerstner, Alois; Nikolakis, Katharina  
 CORPORATE SOURCE: Max-Planck-Institut Kohlenforschung, Muelheim an der Ruhr, D-45470, Germany  
 SOURCE: Liebigs Annalen (1996), (12), 2107-2113  
 CODEN: LANAEM; ISSN: 0947-3440  
 PUBLISHER: VCH  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 126:89204

AB On treatment with B(OMe)<sub>3</sub>, NaOCH undergoes a Pd-catalyzed cross coupling with functionalized aryl halides or triflates in reasonable to good yields. The ethynylarenes thus obtained serve as building blocks for the formation of the highly effective tubulin polymn. inhibitors combretastatin A-4 and A-5 as well as for the synthesis of the plant-growth regulator lunularic acid.

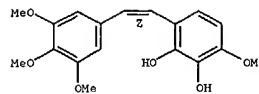
IT 117048-59-6P, Combretastatin A-4  
 RL: SYN (Synthetic preparation); PREP (Preparation)  
 (syntheses of combretastatin A-4, A-5, and lunularic acid via ethynylation of aryl halides by modified Suzuki reaction)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 119 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



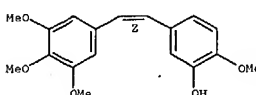
L24 ANSWER 121 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:714628 CAPLUS  
 DOCUMENT NUMBER: 126:628  
 TITLE: Antitumor activity of combretastatin-A4 phosphate, a natural product tubulin inhibitor  
 AUTHOR(S): Dorr, Robert T.; Dvorakova, Katerina; Snead, Kristi; Alberts, David S.; Salmon, Sydney E.; Pettit, G. Robert  
 CORPORATE SOURCE: College Medicine, University Arizona, Tucson, AZ, USA  
 SOURCE: Investigational New Drugs (1996), 14(2), 131-137  
 CODEN: INNDKX; ISSN: 0167-6997  
 PUBLISHER: Kluwer  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The tubulin-binding natural product combretastatin A-4 (CA-4) was tested for antitumor activity against fresh human tumors in vitro and 2 mouse tumors, both in vitro and in vivo. In colony forming assays using 10% fetal bovine serum, CA-4 was inhibitory in 27/40 human ovary cancers with a mean IC50 of 3.18 .mu.g/mL for a 1-h exposure (specimens) and 0.27 .mu.g/mL for a continuous exposure to CA-4 for 11-14 days (specimens). Murine B-16 melanoma and P-388 leukemia were also highly sensitive to CA-4 in vitro with an identical IC50 value of 0.0007 .mu.g/mL for continuous drug exposure for 8 days. Comparable in vitro cell culture studies performed in serum concns. higher than 10%, revealed a significant loss of cytotoxic potency. Using the same reversed-phase HPLC technique as developed for paclitaxel, CA-4 was shown to bind to serum proteins (gtoreq. 30,000 mw) > 99% and to albumin approx. 70%. CA-4 was only marginally active (25% increased lifespan) in DBA/2 mice bearing P-388 leukemia who were given doses of 100 mg/kg IP on either days, 1, 5 and 9 (by Wilcoxon anal.) or on consecutive days 1-9 (compared to control). A higher IP dose of 150 mg/kg on days 1, 5 and 9 did not delay s.c. B-16 melanoma tumor growth in C57/B1 mice. These findings demonstrate a substantial loss of antitumor efficacy for CA-4 in physiol. serum concns. in vitro. No consistent antitumor activity was obsd. in two murine tumor models in vivo.

IT 117048-59-6, Combretastatin-A4  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (antitumor activity of combretastatin-A4 in human tumor cells and in mice)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.





L24 ANSWER 122 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:701793 CAPLUS  
 DOCUMENT NUMBER: 126:69728  
 TITLE: Computational and molecular modeling evaluation of the structural basis for tubulin polymerization inhibition by colchicine site agents  
 AUTHOR(S): ter Haar, Ernst; Rosenkranz, Herbert S.; Hamel, Ernest; Day, Billy W.  
 CORPORATE SOURCE: Dep. Environmental and Occupational Health, Univ. Pittsburgh Cancer Inst., Pittsburgh, PA, 15238, USA  
 SOURCE: Bioorganic & Medicinal Chemistry (1996), 4(10), 1659-1671  
 CODEN: BMECEP; ISSN: 0968-0896  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The computer-automated structure evaluation programs MultiCASE and CASE were used to perform a quant. structure-activity relationship study on tubulin polymn. inhibitors. A learning set of 536 chems. (202 active, 27 marginal, and 307 inactive), built using IC50 values for inhibition of tubulin polymn. or mitosis from this and previous studies, was used for artificial intelligence self-teaching. The algorithms successfully predicted the activity of agents in the learning set with >90% accuracy. Seventeen MultiCASE and 12 CASE (mostly included in the MultiCASE set) biophores (substructures significantly correlated with activity) were identified with a probability >0.95. Here the authors present the biophores of podophyllotoxins, colchicinoids, and certain combretastatins, each examd. for structure-activity relationships. For the podophyllotoxins and colchicinoids in the learning set, the correlations between obsd. and predicted potencies were >0.85. The algorithms recognized the importance of several known site, electronic, and steric effects in the 2 classes. A predictive QSAR (R2 = 0.98) was developed for combretastatin A-2 and dihydrocombretastatin analogs. The MultiCASE/CASE analyses were used in combination with mol. models to study relative orientations of colchicine, podophyllotoxin, combretastatin A-4, and steganacin at the colchicine site. This resulted in a new hypothesis, consistent with extensive published exptl. data, in which the C-ring and part of the B-ring of colchicine overlap with the A- and B-rings of podophyllotoxin. Consequently, the trimethoxyphenyl rings of colchicine and podophyllotoxin occupied different regions of space, each pointing out from a hydrophobic core occupied by the overlapping biophores. The mol. model of the highly potent combretastatin A-4 could fit into the model binding site in .gtorec.3 different ways. The developed QSARs were used to identify the potent microtubule stabilizer discodermolide. Its identification, in concert with recently reported findings, suggest potential overlap in the colchicine and paclitaxel binding sites on tubulin.

IT 117048-59-6  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (computational and mol. modeling evaluation of structural basis for tubulin polymn. inhibition by colchicine site agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

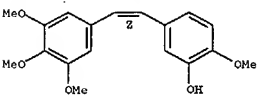
L24 ANSWER 123 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:616598 CAPLUS  
 DOCUMENT NUMBER: 125:309027  
 TITLE: Combretastatin A-4 prodrug  
 INVENTOR(S): Pettit, George R.  
 PATENT ASSIGNEE(S): Arizona State University, USA  
 SOURCE: U.S., 7 pp.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5561122	A	19961001	US 1994-363406	19941222
			US 1994-363406	19941222

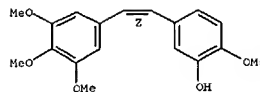
PRIORITY APPLN. INFO.:  
 AB Disclosed herein are combretastatin A4 prodrugs with improved water soly. and stability, for the treatment of one or more neoplastic diseases by means of chemotherapy. Disodium combretastatin A4 3-O-phosphate (I) was prepd. and combretastatin A4 and I demonstrated similar in vitro activity levels in the NCI 60 cell line panel. Formulations contg. the prodrugs are provided.

IT 117048-59-6, Combretastatin A4  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (combretastatin A4 prodrugs and compns. contg. them)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 122 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

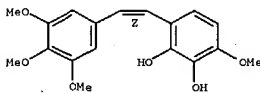


L24 ANSWER 124 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:492720 CAPLUS  
 DOCUMENT NUMBER: 125:185098  
 TITLE: Antivascular approaches to solid tumor therapy: Evaluation of tubulin binding agents  
 AUTHOR(S): Chaplin, DJ; Pettit, GR; Parkins, CS; Hill, SA  
 CORPORATE SOURCE: Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood/Middlesex, HA6 2JR, USA  
 SOURCE: British Journal of Cancer, Supplement (1996), 74(27), S86-S88  
 CODEN: BJCSB5; ISSN: 0306-9443  
 PUBLISHER: Stockton  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB We have assessed the vascular effects of vinblastine and four other tubulin binding agents (dolastatin 10, dolastatin 15, combretastatin A1 and combretastatin A4), which are awaiting clin. evaluation. All five agents induce a redbl. in tumor blood flow as measured by uptake of RbCl 24 h post drug administration. The degree of redbl. ranged from 50% with combretastatin A1 to 90% with dolastatin 10. These redbl. were similar to that seen with flavone acetic acid (FAA) and indicate that antivascular effects are a common feature of tubulin binding agents. We subsequently evaluated whether the blood flow redbl., induced by FAA and vinblastine, could be used to enhance the activity of the bioreductive drug tirapazamine. Since the kinetics and extent of blood flow redbl. induced by the agents is comparable, similar therapeutic response was expected. Potentiation was only evident with FAA, indicating that this effect is not directly related to killing of hypoxic tumor cells induced as a consequence of blood flow redbl.

IT 109971-63-3, Combretastatin A1 117048-59-6, Combretastatin A4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (effect of tubulin binding agents and flavone acetic acid on tumor blood flow and tumor growth)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

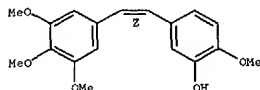
Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 124 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

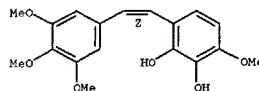


L24 ANSWER 125 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:258929 CAPLUS  
 DOCUMENT NUMBER: 125:25810  
 TITLE: New in vitro screening model for the discovery of antileukemic anticancer agents  
 AUTHOR(S): Valeriote, Frederick; Corbett, Thomas; Edelstein, Mark; Baker, Laurence  
 CORPORATE SOURCE: Harper-Grace Hospitals, Wayne State University, Detroit, MI, 48201, USA  
 SOURCE: Cancer Investigation (1996), 14(2), 124-41  
 CODEN: CINVD7; ISSN: 0735-7907  
 PUBLISHER: Dekker  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

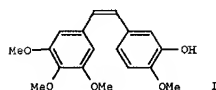
AB The authors describe the in vitro prescreen they have developed and are employing to select for new compds. active against human myelogenous leukemia and they present data from the in vitro screen together with parallel in vivo results. Three sets of compds. were tested: std. clin. employed anticancer agents, a set of purified natural products obtained from the NCI, and a no. of org. synthetic compds. obtained from the Sterling Research Corporation. The data provide a strong affirmation of the screening model to select for agents with in vivo activity.

IT 109971-63-3, Combretastatin A-1  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (new in vitro screening model for discovery of antileukemic anticancer agents)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

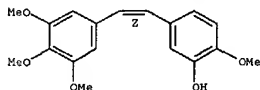


L24 ANSWER 126 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1996:108637 CAPLUS  
 DOCUMENT NUMBER: 124:260682  
 TITLE: Synthesis of water-soluble prodrugs of the cytotoxic agent combretastatin A4  
 AUTHOR(S): Bedford, Simon B.; Quarterman, Charmaine P.; Rathbone, Daniel L.; Slack, John A.; Griffin, Roger J.; Stevens, Malcolm F. G.  
 CORPORATE SOURCE: Aston Molecules Ltd., Birmingham, B7 4EY, UK  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(2), 157-60  
 CODEN: BMCLES; ISSN: 0960-894X  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB Water-sol. phosphate and glycine carbamate prodrugs of the cytotoxic agent Combretastatin A4 (1) have been prepd. The phosphate prodrug was degraded slowly in plasma at 37.degree.C. The degradn. was accelerated by the addn. of alk. phosphatase.  
 IT 117048-59-6P, Combretastatin A4  
 RL: SEN (Synthetic preparation); PREP (Preparation)  
 (synthesis of water-sol. prodrugs of the cytotoxic agent combretastatin A4)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

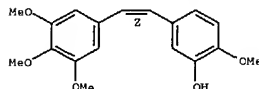


L24 ANSWER 127 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:923441 CAPLUS  
 DOCUMENT NUMBER: 124:209907  
 TITLE: Inhibition of [3H]mebendazole binding to tubulin by structurally diverse microtubule inhibitors which interact at the colchicine binding site  
 AUTHOR(S): Russell, Gregory J.; Lacey, Ernest  
 CORPORATE SOURCE: Dep. of Veterinary Pathology, Univ. of Sydney, 2006, Australia  
 SOURCE: Biochemistry and Molecular Biology International (1995), 35(6), 1153-9  
 CODEN: BMBIES; ISSN: 1039-9712  
 PUBLISHER: Academic  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB A rapid and convenient radioligand assay was used to characterize the interaction of several structurally diverse microtubule inhibitors with the colchicine binding domain of tubulin. Values detd. for the inhibition of [3H]mebendazole binding to tubulin by colchicine, combretastatin A4, NSC 181928, NSC 321567, podophyllotoxin and tubulozole-C provided an independent measure of the relative potency of these compds. This methodol. has several advantages over the inhibition of [3H]colchicine binding as a technique for investigating the mol. mechanisms involved in detg. tubulin-ligand interactions.

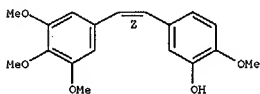
IT 117048-59-6, Combretastatin A4  
 RL: RAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (inhibition of [3H]mebendazole binding to tubulin by structurally diverse microtubule inhibitors which interact at the colchicine binding site)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



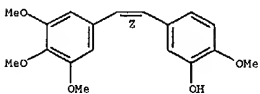
L24 ANSWER 128 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:846307 CAPLUS  
 DOCUMENT NUMBER: 123:30598  
 TITLE: Characterization of the interaction of the marine cyanobacterial natural product curacin A with the colchicine site of tubulin and initial structure-activity studies with analogs  
 AUTHOR(S): Blokhin, Andrei V.; Yoo, Hye-Dong; Geraldes, Robin S.; Nagle, Dale G.; Gerwick, William H.; Hamel, Ernest  
 CORPORATE SOURCE: Lab. Mol. Pharmacology, Developmental Therapeutics Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA  
 SOURCE: Molecular Pharmacology (1995), 48(3), 523-31  
 CODEN: MOPMA3; ISSN: 0026-895X  
 PUBLISHER: Williams & Wilkins  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Curacin A, the major lipid constituent of a strain of the marine cyanobacterium *Lyngbya majuscula* obtained off the coast of Curacao, is a potent antimitotic agent that we have previously shown to inhibit microtubule assembly and colchicine binding to tubulin. In the present study, we report that curacin A probably binds in the colchicine site because it competitively inhibits the binding of [<sup>3</sup>H]colchicine to tubulin with an apparent K<sub>i</sub> value of 0.6 μM and stimulates tubulin-dependent GTP hydrolysis, as do most other colchicine-site agents. The binding of curacin A to tubulin resembled the binding reactions of combretastatin A-4 and podophyllotoxin in contrast to that of colchicine in that it occurred as extensively on ice as at higher temps. However, once bound, the disocn. rate of curacin A from tubulin was very slow, more closely resembling that obsd. with colchicinoids (thiocolchicine was the drug examd.) than the faster disocn. that occurs with the combretastatin A-4 and podophyllotoxin. Because the mol. structure of curacin A is so different from that of previously described colchicine-site drugs (e.g., there is no arom. moiety, and there are only two conjugated double bonds in its linear hydrocarbon chain), we have been examg. the activities of natural isomers and synthetic derivs. So far, only modest enhancement or redn. of activity has been obsd. with a variety of structural changes.  
 IT 117048-59-6, Combretastatin A4  
 RI: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
 (Interaction of curacin A and analogs with colchicine site of tubulin)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 129 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:741422 CAPLUS  
 DOCUMENT NUMBER: 124:116940  
 TITLE: Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6. [Erratum to document cited in CA122:290568]  
 AUTHOR(S): Pettit, George R.; Singh, Sheo Bux; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Schmidt, Jean M.; Hogan, Fiona  
 CORPORATE SOURCE: Cancer Research Institute and Dept. of Chemistry, Arizona State Univ., Tempe, AZ, 85287-1604, USA  
 SOURCE: Journal of Medicinal Chemistry (1995), 38(15), 2994  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The errors were not reflected in the abstr. or the index entries.  
 IT 117048-59-6P, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
 (Isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6 (Erratum))  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

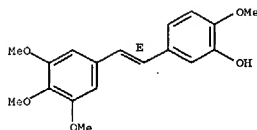


IT 117048-62-1P  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (Isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6 (Erratum))  
 RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

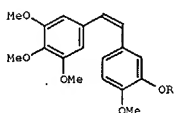
Double bond geometry as shown.

L24 ANSWER 128 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 129 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 130 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:661775 CAPLUS  
 DOCUMENT NUMBER: 123:227731  
 TITLE: Antineoplastic agents. 322. Synthesis of combretastatin A-4 prodrugs  
 AUTHOR(S): Pettit, George R.; Temple, Carroll, Jr.; Narayanan, Ven L.; Varma, Ravi; Simpson, Michael J.; Boyd, Michael R.; Rener, Gregory A.; Bansal, Namita  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA  
 SOURCE: Anti-Cancer Drug Design (1995), 10(4), 299-309  
 CODEN: ACDEA; ISSN: 0266-9536  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB Combretastatin A-4 (I, R = H), the principal cancer cell growth-inhibitory constituent of the Zulu medicinal plant (*Combretum caffrum*, has been undergoing preclin. development. However, the very limited water soly. of this phenol has complicated drug formulation. Hence, derivs. of the combretastatin A-4 3'-phenol group were prepd. for evaluation as possible water-sol. prodrugs. As obsd. for combretastatin A-4, the sodium salt (I, R = Na), potassium salt (I, R = K), and hemisuccinic acid ester (I, R = COCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H) derivs. were essentially insol. in water. Indeed, these substances regenerated combretastatin A-4 upon reaction with water. A series of other simple derivs., e.g. I [R = COCH<sub>2</sub>(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H], proved unsatisfactory in terms of water soly. or stability, or both. The most sol. derivs. evaluated included the ammonium [I, R = P(O)(OH)CNH<sub>4</sub>], and potassium [I, R = P(O)(OK)<sub>2</sub>] and sodium [I, R = P(O)(ONa)<sub>2</sub>] phosphate salts, where the latter two proved most stable and suitable. Both the potassium and sodium phosphate derivs. of combretastatin A-4 were also found to exhibit the requisite biol. properties necessary for a useful prodrug. The sodium phosphate salt was selected for drug formulation and further pre-clin. development.

IT 117048-59-6, Combretastatin A-4  
 RI: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis of combretastatin A-4 prodrugs as antineoplastic agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

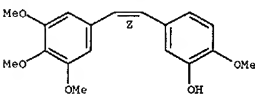
Double bond geometry as shown.

L24 ANSWER 131 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:619726 CAPLUS  
 DOCUMENT NUMBER: 123:47372  
 TITLE: The interaction with tubulin of a series of stilbenes based on combretastatin A-4  
 AUTHOR(S): Woods, J.A.; Hadfield, J.A.; Pettit, G.R.; Fox, B.W.; McGown, A.T.  
 CORPORATE SOURCE: Paterson Institute Cancer Research, Christie Hospital, Manchester, M20 9BX, UK  
 SOURCE: British Journal of Cancer (1995), 71(4), 705-11  
 CODEN: BJCAAI; ISSN: 0007-0920  
 PUBLISHER: Journal  
 DOCUMENT TYPE: English  
 LANGUAGE: English

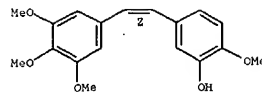
AB A series of stilbenes, based on combretastatin A-4, were synthesized. A structure-activity study was carried out to characterize the interaction of these agents with tubulin. The substitution of small alkyl substituents for the 4'-MeO group of combretastatin A-4 and the loss of the 3'-OH group does not have a major effect on the interaction with tubulin. Trans-Stilbenes bound tubulin, but did not inhibit microtubule assembly. An idealized structure for a tubulin-binding agent of this type is proposed. The antitumor cytotoxicity of the compds. is also discussed.

IT 117048-59-6DP, Combretastatin A-4, analogs  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRE (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (interaction of combretastatin A-4-related stilbenes with tubulin)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

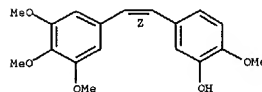


L24 ANSWER 130 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 168555-63-3P 168555-67-7P  
 RI: SPN (Synthetic preparation); PREP (Preparation)  
 (synthesis of combretastatin A-4 prodrugs as antineoplastic agents)  
 RN 168555-63-3 CAPLUS  
 CN Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, sodium salt, (2)- (9CI) (CA INDEX NAME)

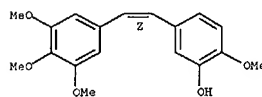
Double bond geometry as shown.



• Na

RN 168555-67-7 CAPLUS  
 CN Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, potassium salt, (2)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



• K

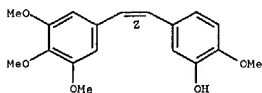
L24 ANSWER 132 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:538890 CAPLUS  
 DOCUMENT NUMBER: 122:290568  
 TITLE: Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6  
 AUTHOR(S): Pettit, George R.; Singh, Shao Bux; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Schmidt, Jean M.; Hogan, Fiona  
 CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA  
 SOURCE: Journal of Medicinal Chemistry (1995), 38(10), 1666-72  
 CODEN: JMCHAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The title compds. (2)-3,4,5-(MeO)3C6H2CH=CHC6H3(OMe)OH-4,3 (I) and (Z)- and (E)-3,4,5-HO(MeO)2C6H2CH=CHC6H3(OMe)2-3,4 (II) were isolated from *Combretum caffrum*. They were also prepd. by Wittig reactions. I is the most potent cell growth inhibitor of the series. It is also the most potent inhibitor of colchicine binding to tubulin. I and II also inhibit the growth of *Neisseria gonorrhoeae*, but have no fungicidal activity.

IT 117048-59-6P, Combretastatin A-4  
 RI: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRE (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)  
 (isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

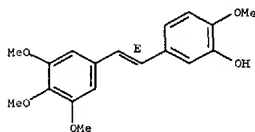
Double bond geometry as shown.



IT 117048-62-1P  
 RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6)  
 RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 132 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



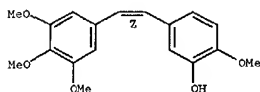
L24 ANSWER 133 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:532227 CAPLUS  
 DOCUMENT NUMBER: 122:256433  
 TITLE: Estrogens as antimitotic agents  
 INVENTOR(S): D'Amato, Robert John; Folkman, Moses Judah  
 PATENT ASSIGNEE(S): Children's Medical Center Corp., USA  
 SOURCE: PCT Int. Appl., 53 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9504535	A1	19950216	WO 1994-US8767	19940802
W:	AM, AT, AU, BE, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN			
RW:	KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GH, ML, HR, NE, SN, TD, TG			
US 5504074	A	19960402	US 1993-102767	19930806
CA 2168850	AA	19950216	CA 1994-2168850	19940802
AU 9474509	A1	19950228	AU 1994-74509	19940802
EP 713393	A1	19960529	EP 1994-924120	19940802
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE			
JP 09501433	T2	19970210	JP 1994-506502	19940802
US 5661143	A	19970826	US 1995-571265	19951212
US 5892069	A	19990406	US 1997-838699	19970425
US 6528676	B1	20030304	US 1999-243158	19990202
US 2002165212	A1	20021107	US 2002-77142	20020215
US 2002119959	A1	20020829	US 2002-80076	20020221
US 2003055029	A1	20030320	US 2002-255652	20020925
US 2003098800	A1	20030522	US 2002-280831	20021025
PRIORITY APPLN. INFO.:			US 1993-102767	A 19930806
			WO 1994-US8767	W 19940802
			US 1995-571265	A3 19951212
			US 1997-838699	A3 19970425
			US 1998-19975	B1 19980206
			US 1999-243158	B1 19990202
			US 1999-436610	B1 19991109
			US 2000-580897	A1 20000530
			US 2001-780650	A1 20010212

OTHER SOURCE(S): MARPAT 122:256433  
 AB Drugs for treating mammalian diseases characterized by abnormal cell mitosis by administering estradiol derivs., colchicine or combretastatin A-4 are described. The inhibition of tubulin polym. by 2-methoxyestradiol (75 .mu.M) in a mixt. contg. monosodium glutamate, DMSO and MgCl2 was demonstrated.  
 IT 117048-59-6, Combretastatin A-4  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (estrogens as antimitotic agents)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 133 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

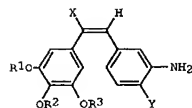
Double bond geometry as shown.



L24 ANSWER 134 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:520466 CAPLUS  
 DOCUMENT NUMBER: 122:265183  
 TITLE: Preparation of stilbene derivatives as carcinostatic agents.  
 INVENTOR(S): Ohsumi, Koji; Tsuji, Takashi; Morinaga, Yoshihiro;  
 Ohishi, Kazuo  
 PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan  
 SOURCE: Eur. Pat. Appl., 14 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 641767	A1	19950308	EP 1994-306522	19940905
EP 641767	B1	19981223		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE			
AT 174899	E	19990115	AT 1994-306522	19940905
ES 2128068	T3	19990316	ES 1994-306522	19940905
JP 0728558	A2	19950829	JP 1994-236046	19940906
JP 2045017	B2	20000522		
CA 2131683	AA	19950309	CA 1994-2131683	19940908
CN 1105967	A	19950802	CN 1994-116204	19940908
CN 1035996	B	19971001		
US 5525632	A	19960611	US 1994-302210	19940908
US 5731353	A	19980324	US 1996-613005	19960308
PRIORITY APPLN. INFO.:			JP 1993-223573	A 19930908
			JP 1993-322832	A 19931221
			US 1994-302210	A1 19940908

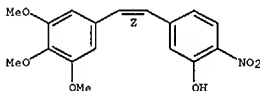
OTHER SOURCE(S): CASREACT 122:265183; MARPAT 122:265183  
 GI



AB The prepn. of stilbenes I (R1, R2, R3 = C1-3 alkyl; X = H, cyano; Y = C1-3 alkyloxy, C1-6 alkyl, halo), which are low in toxicity, but are water sol. and effective as carcinostatics, is described. Thus, stilbene I (R1 = R2 = R3 = Me, X = H, Y = MeO), prepd. by condensation of 4-methoxy-3-nitrobenzaldehyde with 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and subsequent reduct. of the nitro group, inhibited the growth of mouse P388 leukemia cells with an IC50 = 0.2 ng/mL (comparable to combretastatin A-4).  
 IT 117048-59-6DP, Combretastatin A-4, analogs  
 RL: BAC (Biological activity or effector, except adverse); RSU (Biological study, unclassified); SFM (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of stilbene derivs. as carcinostatic agents)  
 RN 117048-59-6 CAPLUS

L24 ANSWER 137 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1995:21047 CAPLUS  
 DOCUMENT NUMBER: 122:81695  
 TITLE: Potential Photoaffinity Labels for Tubulin. Synthesis and Evaluation of Diazocyclohexadienone and Azide Analogs of Colchicine, Combrétastatin, and 3,4,5-Trimethoxybiphenyl  
 AUTHOR(S): Olszewski, John D.; Marshalla, Mary; Sabat, Michal; Sundberg, Richard J.  
 CORPORATE SOURCE: Department of Chemistry, University of Virginia, Charlottesville, VA, 22901, USA  
 SOURCE: Journal of Organic Chemistry (1994), 59(15), 4285-96  
 CODEN: JOCEAH; ISSN: 0022-3263  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB: Analogs of tubulin assembly inhibitors such as colchicine, combrétastatin, and 3,4,5-trimethoxybiphenyl which incorporate a 6-diazo-2,4-cyclohexadienone (o-quinone diazide) ring have been synthesized and characterized. Compds. in which the cyclohexadienone oxygen is approx. isostructural with carbonyl or hydroxy functions of the parent compds. exhibit good activity in the tubulin assembly inhibition assay. 2'-Allyl-4'-azido-3,4,5-trimethoxy-1,1'-biphenyls also show good activity as tubulin assembly inhibitors.  
 IT 156878-52-3P 156878-53-4P 156878-54-5P  
 RI: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. and reaction of, in prepn. of diazocyclohexadienone-contg. tubulin assembly inhibitors)  
 RN 156878-52-3 CAPLUS  
 CN Phenol, 2-nitro-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

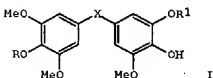


RN 156878-53-4 CAPLUS  
 CN Phenol, 2-nitro-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

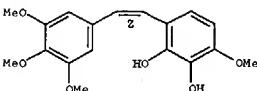
L24 ANSWER 138 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1994:473872 CAPLUS  
 DOCUMENT NUMBER: 121:73872  
 TITLE: Combrétastatin derivatives with antitumor activity, and process for the preparation thereof  
 INVENTOR(S): Felizzoni, Francesca; Colombo, Roberto; D'Incalci, Maurizio; Verotta, Luisa  
 PATENT ASSIGNER(S): Italy  
 SOURCE: PCT Int. Appl., 28 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:  

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9405682	A1	19940317	WO 1993-EP2173	19930816
W: AU, BY, CA, FI, HU, JP, KR, KZ, NZ, PL, RU, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9349479	A1	19940329	AU 1993-49479	19930816
ZA 9306311	A	19940323	ZA 1993-6311	19930827
PRIORITY APPLN. INFO.: IT 1992-M12033 A 19920831				
WO 1993-EP2173 W 19930816				
OTHER SOURCE(S): MARPAT 121:73872				
GI				



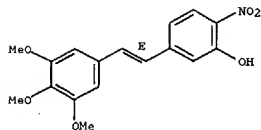
AB Combrétastatin derivs. I (R = H, Me; R' = H, .beta.-D-glucopyranose (provided that when R is Me, R' .noteq. H); A = CH2CH2, CH:CH) with antitumor activity are disclosed. Also included are a process for the extn. and isolation of I from Combrétum kraussii, pharmaceutical compns. for antitumor use, and prepn. of the pharmaceutical compns.  
 IT 109971-63-3P 156085-79-9P  
 RI: PUR (Purification or recovery); PREP (Preparation)  
 (isolation of, from Combrétum kraussii, for antitumor agent)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

Double bond geometry as shown.



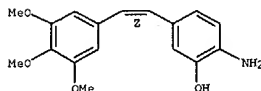
RN 156085-79-9 CAPLUS

L24 ANSWER 137 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



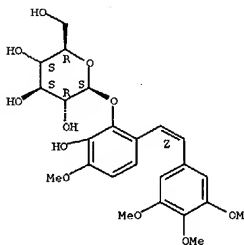
RN 156878-54-5 CAPLUS  
 CN Phenol, 2-amino-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 138 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).  
 Double bond geometry as shown.

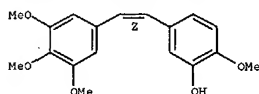


L24 ANSWER 139 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1994:473249 CAPLUS  
 DOCUMENT NUMBER: 121:73249  
 TITLE: Increase in the chemically-induced differentiation of human leukemia cell lines by tubulin disruptors  
 AUTHOR(S): Nakajima, Osamu; Sugishita, Yasuko; Hashimoto, Yuichi; Iwasaki, Shigeo  
 CORPORATE SOURCE: Inst. Mol. Cellular Biosciences, University Tokyo, Tokyo, 113, Japan  
 SOURCE: Biological & Pharmaceutical Bulletin (1994), 17(5), 742-4  
 CODEN: BPBLEO; ISSN: 0918-6158  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The effect of various structural functional tubulin disruptors (including colchicine-type disruptors, vinblastine, rhizoxin, maytansine, peptide-type disruptors, and taxol) on the chem. induced differentiation of human leukemia cell lines (HL-60 and K562) was examd. As differentiation-inducing agents, 12-O-tetradecanoylphorbol-13-acetate (TPA) was used for the differentiation of both HL-60 and K562 to monocyte/macrophages, retinoids were used for the differentiation of HL-60 to mature granulocytes, and hemin was used for the erythroid differentiation of K562. All the tubulin disruptors investigated increased the chem.-induced differentiation of HL-60 and K562 cell lines to the cognate mature cell types, regardless of the nature of the differentiation.

IT 117048-59-6, Combretastatin A-4  
 RL: BIOL (Biological study)  
 (chem. induced leukemia cell differentiation increase by, of humans, as tubulin disruptor)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

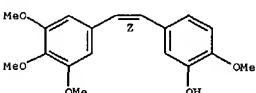


L24 ANSWER 141 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1994:290371 CAPLUS  
 DOCUMENT NUMBER: 120:290371  
 TITLE: 2-Methoxyestradiol, an endogenous mammalian metabolite, inhibits tubulin polymerization by interacting at the colchicine site  
 AUTHOR(S): D'Amato, Robert J.; Lin, Chii M.; Flynn, Evelyn; Folkman, Judah; Hamel, Ernest  
 CORPORATE SOURCE: Dep. Surg. Res., Harvard Med. Sch., Boston, MA, 02115, USA  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1994), 91(9), 3964-8  
 CODEN: PNASAA; ISSN: 0027-8424  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

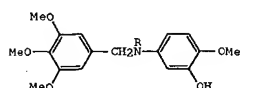
AB A metabolite of estradiol, 2-methoxyestradiol (2ME), inhibits angiogenesis in the chicken embryo chorioallantoic membrane assay. Since 2ME causes mitotic perturbations, the authors examd. its interactions with tubulin. In the authors' std. 1.0M glutamate system (plus 1.0 mM MgCl2 at 37.degree.), superstoichiometric concns. (relative to tubulin) of 2ME inhibited the nucleation and propagation phases of tubulin assembly but did not affect the reaction extent. Although polymer formed in the presence of 2ME was more cold-stable than control polymer, morphol. was little changed. Under suboptimal reaction conditions (0.8M glutamate/no MgCl2 at 26.degree.), substoichiometric 2ME totally inhibited polymn. No other estrogenic compd. was as effective as 2ME as an inhibitor of polymn. or of the binding of colchicine to tubulin. Inhibition of colchicine binding was competitive (Ki, 22 .mu.M). Thus, a mammalian metabolite of estradiol binds to the colchicine site of tubulin and, depending on reaction conditions, either inhibits assembly or seems to be incorporated into a polymer with altered stability properties.

IT 117048-59-6, Combretastatin A-4  
 RL: BIOL (Biological study)  
 (tubulin polymn. inhibition by)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



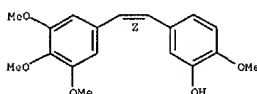
L24 ANSWER 140 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1994:426244 CAPLUS  
 DOCUMENT NUMBER: 121:26244  
 TITLE: Synthesis and anti-tubulin activity of 3,4,5-combretastatins  
 AUTHOR(S): Shirai, Ryuichi; Tokuda, Kazuyoshi; Kniso, Yukiko; Iwasaki, Shigeo  
 CORPORATE SOURCE: Inst. Mol. Cell. Biosci., Univ. Tokyo, Tokyo, 113, Japan  
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(5), 699-704  
 CODEN: BMCLE8; ISSN: 0960-894X  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English



AB A series of 3,4,5-combretastatins was synthesized and their activity against microtubule assembly was evaluated. N-benzylaniline analogs with a variety of side chains (I, R = e.g., H or alkyl) showed moderate to excellent inhibitory activity while benzanilide analogs had little activity.

IT 117048-59-6, Combretastatin A-4  
 RL: RAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (antitubulin activity of, 3,4,5 analogs in relation to)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



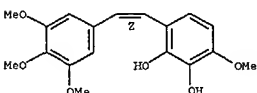
L24 ANSWER 142 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1993:621659 CAPLUS  
 DOCUMENT NUMBER: 119:221659  
 TITLE: Cell growth inhibitor constituents from Combretum krasussii  
 AUTHOR(S): Felizzoni, F.; Verotta, L.; Rogers, C. B.; Colombo, R.; Pedrotti, B.; Balconi, G.; Erba, E.; D'Incalci, M.  
 CORPORATE SOURCE: Dip. Chim. Org. IND., Milano, 20133, Italy  
 SOURCE: Natural Product Letters (1993), 1(4), 273-80  
 CODEN: NPLERF; ISSN: 1057-5634  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB New and known combretastatins and their 2'-O-glucosides have been isolated from seeds of Combretum krasussii (Hochst.) (Combretaceae). They showed in vitro cytotoxicity and influenced the tubulin polymn.

IT 109971-63-3 150934-29-5  
 RL: BIOL (Biological study)  
 (from Combretum krasussii, isolation and structure of)

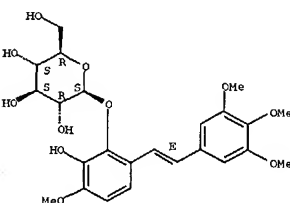
RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 150934-29-5 CAPLUS  
 CN beta-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl, (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.

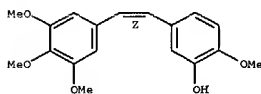


L24 ANSWER 143 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1993:225093 CAPLUS  
 DOCUMENT NUMBER: 118:225093  
 TITLE: In vitro evaluation of the antineoplastic activity of combretastatin A4, a natural product from Combretum caffrum (arid shrub)  
 AUTHOR(S): El-Zayat, A. Atef Ebrahim; Degen, Donna; Drabek, Sonya; Clark, Gary M.; Pettit, George R.; Von Hoff, Daniel D.  
 CORPORATE SOURCE: Cancer Ther. Res. Cent., San Antonio, TX, 78229, USA  
 SOURCE: Anti-Cancer Drugs (1993), 4(1), 19-25  
 CODEN: ANTDEV; ISSN: 0959-4973  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

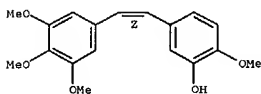
AB The cytotoxic activity of combretastatin A4 was tested in radiometric and human tumor cloning assays against 8 different tumor cell lines and against 15 patient tumors in the human tumor cloning assay. To test the preferential cytotoxicity of combretastatin A4 against tumor cells vs. nontumor cells, it was also tested in the radiometric assay against both normal human diploid fibroblasts and human bone marrow cells. Of the 8 cell lines used, combretastatin A4 showed preferential cytotoxicity for six of them. In addn., combretastatin A4 showed a concn.-dependent cytotoxicity against a variety of human tumors. Based on these data, combretastatin A4 should be further tested in in vivo preclin. models.  
 IT 117048-59-6, Combretastatin A4  
 RL: BIOL (Biological study)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

Double bond geometry as shown.

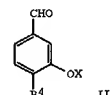
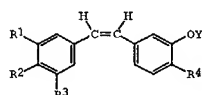


L24 ANSWER 144 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 Double bond geometry as shown.



L24 ANSWER 144 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1993:101642 CAPLUS  
 DOCUMENT NUMBER: 118:101642  
 TITLE: Preparation of combretastatin A4 analogs as neoplasm inhibitors  
 INVENTOR(S): Rathbone, Daniel Lee; Slack, John Alfred; Griffin, Roger John; Quarterman, Charmaine Paulina  
 PATENT ASSIGNEE(S): Aston Molecules Ltd., UK  
 SOURCE: PCT Int. Appl., 29 pp.  
 CODEN: PFXKD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

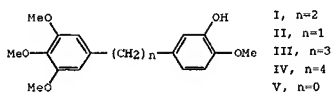
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9216486	A1	19921001	WO 1992-GB498	19920319
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9213719	A1	19921021	AU 1992-13719	19920319
PRIORITY APPL. INFO.:			GB 1991-6177	19910322
			WO 1992-GB498	19920319
OTHER SOURCE(S):		MARPAT 118:101642		
GI				



AB Title compds. I [R1-R4 = alkoxy; Y = H, phosphate, phosphate deriv., amino acid carbamate, carbonylhydrazide deriv., polyhydroxylated group] were prepd. via Wittig olefination of benzaldehyde deriv. II (X = protecting group) by a trialkoxybenzylphosphonium halide. I, e.g., water sol. combretastatin A4 analogs, are neoplasm inhibitors (no data). Thus, 3-hydroxy-4-methoxybenzaldehyde was protected by thenyldimethylsilyl chloride then olefinated by 3,4,5-trimethoxybenzylphosphonium bromide (prepn. given). The product was deprotected by Bu4NF to give combretastatin A4. This was treated with di-tert-Bu N,N-diethylphosphoramidite and 1H-tetrazole in THF, cooled to -70.degree., then treated, with MCPBA to give combretastatin A4 phosphate bis(tert-butyl) ester in 77% yield.  
 IT 117048-59-6  
 RL: RAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of, as neoplasm inhibitor)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

L24 ANSWER 145 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1992:143282 CAPLUS  
 DOCUMENT NUMBER: 116:143282  
 TITLE: Synthesis of alkoxy-substituted diaryl compounds and correlation of ring separation with inhibition of tubulin polymerization: differential enhancement of inhibitory effects under suboptimal polymerization reaction conditions  
 AUTHOR(S): Getahun, Zelleke; Jurd, Leonard; Chu, Ping S.; Lin, Chii M.; Hamal, Ernest  
 CORPORATE SOURCE: Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA  
 SOURCE: Journal of Medicinal Chemistry (1992), 35(6), 1058-67  
 CODEN: JMCHAR; ISSN: 0022-2623  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



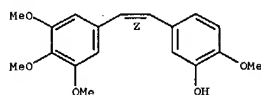
AB A no. of cytostatic compds. which can be described as diaryl, inhibit tubulin polymn., cause cells to accumulate in mitotic arrest, and competitively inhibit the binding of colchicine to tubulin. They differ, however, in the sepn. of the 2 aryl moieties. To attempt to understand this variability a series of analogs modeled on a benzodioxole series and on a combretastatin series which differed only in the no. of methylene units (ranging from 0-4) sepy. the aryl moieties were prepd. These compds. were evaluated for their effects on tubulin polymn., colchicine binding, and the growth of L1210 murine leukemia cells. In terms of inhibitory effects on tubulin polymn., for the combretastatin series there was an optimal sepn. of the 2 Ph rings by a 2-carbon bridge (I), with progressively decreasing inhibitory activity when the sepn. was by 1 carbon (II), 3 carbons (III), or 4 carbons (IV) (the biphenyl analog V was inactive). The benzodioxole series, however, did not permit the generalization of this finding, because the least active agents prepd. had a 2-carbon bridge, while those with 1 and 3-carbon bridges were nearly equiv. in potency. Submicromolar IC50 values for inhibition of L1210 cell growth were only obtained for II (IC50, 0.2 .mu.M), I (0.07 .mu.M), and III (0.4 .mu.M). While evaluating the effects of these agents on tubulin polymn., with the combretastatin series and with several std. agents apparent potency (in terms of IC50 values) was always lower if the reaction was performed at 30.degree., with 0.25 mM MgCl2, than at 37.degree., with 1.0 mM MgCl2. This enhancement of IC50 values in the former system as compared with the latter was particularly dramatic for the less active agents (e.g., IV) as compared with the more active (e.g., I).

IT 117048-59-6, Combretastatin A-4  
 RL: BIOL (Biological study)  
 (Binding of colchicine to and polymn. of tubuline inhibition by)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)



L24 ANSWER 145 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

Double bond geometry as shown.



L24 ANSWER 146 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:75795 CAPLUS  
DOCUMENT NUMBER: 116:75795

TITLE: Investigation of the mechanism of the interaction of tubulin with derivatives of 2-styrylquinazolin-4(3H)-one

AUTHOR(S): Lin, Chii M.; Kang, Gil Jong; Roach, Mary Carmen; Jiang, Jack B.; Hesson, David P.; Duduena, Richard F.; Hamel, Ernest

CORPORATE SOURCE: Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA

SOURCE: Molecular Pharmacology (1991), 40(5), 827-32

CODEN: MOFMA3; ISSN: 0026-895X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new class of antimitotic agents, derivs. of 2-styrylquinazolin-4(3H)-one (SQZ), was recently described [J. Med. Chem. 33:1721-1728 (1990)]. Because they appeared to interact at a new ligand binding site on tubulin, the authors attempted to det. their mechanism of action as inhibitors of tubulin polymn. Although in initial studies inhibition of colchicine binding was negligible, substantial and competitive inhibition of this reaction could be demonstrated with very short incubation times (<5 min), provided that a relatively low colchicine to tubulin ratio was used. The initial apparent failure to inhibit colchicine binding resulted from extremely rapid binding to tubulin and dissocn. from tubulin by the SQZ deriva., in comparison with the slow, temp.-dependent, poorly reversible binding of colchicine. The most inhibitory of the SQZ derivs. in the colchicine binding assay was 6-methyl-2-styrylquinazolin-4(3H)-one (NSC 379310), and its interaction with tubulin, particularly as an inhibitor of colchicine binding, was compared with that of 2-methoxy-5-(2',3',4'-trimethoxyphenyl) tropone (MTPT), because the binding parameters of MTPT with tubulin have been well described. The data indicate that NSC 379310 binds to tubulin and dissoc. from the protein about 3 times as rapidly as MTPT. The other SQZ deriva. with equal or greater potency as inhibitors of tubulin polymn. but apparently less potency as inhibitors of colchicine binding presumably bind to and/or dissoc. from tubulin even more rapidly than does NSC 379310.

IT 117048-59-6

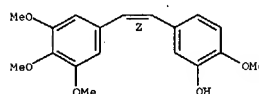
RL: BIOL (Biological study)

(tubulin binding inhibition by, antimitotic mechanism in relation to)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 147 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:589740 CAPLUS

DOCUMENT NUMBER: 115:189740

TITLE: Combretastatin A-4 from Combretum cafferum

INVENTOR(S): Pettit, George R.; Singh, Sheo E.

PATENT ASSIGNEE(S): Arizona Board of Regents, USA

SOURCE: U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 590.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

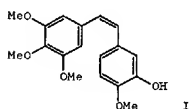
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4996237	A	19910226	US 1988-158866	19880222
CA 1338645	A1	19961015	CA 1987-554733	19871217
JP 63233939	A2	19880929	JP 1987-327577	19871225
JP 2558131	B2	19961127		
ES 2038747	T3	19930801	ES 1988-300064	19880106
US 5409953	A	19950425	US 1992-832998	19920210
US 5569786	A	19961029	US 1994-340156	19941115

PRIORITY APPLN. INFO.:

US 1987-590 19870106

US 1992-832998 19920210

GI



AB Combretastatin A-4 (I) is extd. from the stem wood of C. cafferum. I is a powerful inhibitor of tubulin polymn. (IC50 2-3 μM) and of the growth of murine lymphocytic leukemia (L1210 and P388; ED50 <0.003 mg/mL) and human colon cancer cell lines (Volo, etc.; ED50 <0.01 μM/g/mL). The structure assigned by spectral techniques was confirmed by synthesis. Capsule, tablet, powder, parenteral, and other formulations are presented.

IT 117048-59-6P, Combretastatin A-4

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and isolation of, from Combretum cafferum, as neoplasm inhibitor)

RN 117048-59-6 CAPLUS

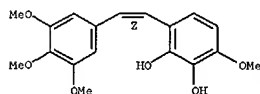
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 148 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1991:484835 CAPLUS  
 DOCUMENT NUMBER: 115:84835  
 TITLE: Quantitative structure-activity relationship analysis of combretastatins: a class of novel antimitotic agents  
 AUTHOR(S): Nandy, Partha; Banerjee, Samitendu; Gao, Hua; Hui, Mary B. V.; Lien, Eric J.  
 CORPORATE SOURCE: Sch. Pharm., Univ. South. California, Los Angeles, CA, 90033, USA  
 SOURCE: Pharmaceutical Research (1991), 8(6), 776-81  
 CODEN: PHREB; ISSN: 0724-8741  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Combretastatins and their synthetic analogs had structural features resembling those of colchicine and also have similar modes of action. The cytotoxicity of combretastatins against the murine leukocyte cell line L1210 was correlated with physicochem. parameters such as the summation of the Hansch-Fujita .pi. const., which was used as an index of lipophilicity of the substituent groups on ring A (.SIGMA.pi.a) and ring B (.SIGMA.pi.b), the vector summation of the group dipole moments of ring A (.SIGMA.mu.a) and ring B (.SIGMA.mu.b), the nature of the linker chain between ring A and ring B (Bt-L), indicator parameters (NOH)a and (NOH)b, which represent the no. of hydroxyl groups on ring A and ring B, resp., and the summation of .pi. values of the substituents on the linker (.SIGMA.pi.L). Cytotoxicity correlated well with (.SIGMA.pi.b), (NOH)a, (Bt-L), and (.SIGMA.mu.b), and the dependency on (.SIGMA.pi.b) was parabolic.  
 IT 109971-63-3 117048-59-6 117048-62-1  
 RL: BIOL (Biological study)  
 (antileukemic cytotoxicity and structure of)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

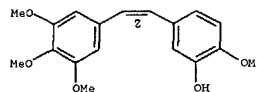
Double bond geometry as shown.



RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

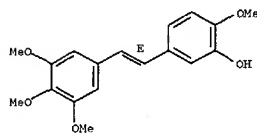
Double bond geometry as shown.

L24 ANSWER 148 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

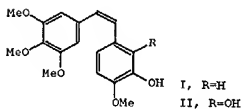


RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



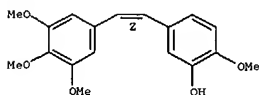
L24 ANSWER 149 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1990:400240 CAPLUS  
 DOCUMENT NUMBER: 113:240  
 TITLE: Differential cytotoxicity of combretastatins A1 and A4 in two daunorubicin-resistant F388 cell lines  
 AUTHOR(S): McGown, Alan T.; Fox, Brian W.  
 CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp., Withington/ Manchester, M20 9EX, UK  
 SOURCE: Cancer Chemotherapy and Pharmacology (1990), 26(1), 79-81  
 CODEN: CCRPHD; ISSN: 0344-5704  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB Combretastatin A4 (I), a novel antimitotic agent was effective against two F388 cell lines with acquired resistance to daunorubicin. In contrast, combretastatin A1 (II) showed a high degree of cross-resistance. II was also more efficient at increasing intracellular daunorubicin concns. in both resistant cell lines. Neither agent was capable of altering anthracycline accumulation in the parental (sensitive) cell line. The cross-resistance to II occurs, at least in part, as a result of the increased affinity of the drug-efflux process operative in these resistant cells for II vs. I. Hence, I may play a role in the treatment of tumors with acquired resistance to the anthracycline antibiotics.  
 IT 117048-59-6, Combretastatin A4  
 RL: FRP (Properties)  
 (cytotoxicity of, to multidrug-resistant tumor cell lines, combretastatin A1 in relation to)

RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

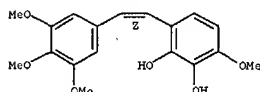
Double bond geometry as shown.



IT 109971-63-3, Combretastatin A1  
 RL: FRP (Properties)  
 (cytotoxicity of, to multidrug-resistant tumor cell lines, combretastatin A4 in relation to)  
 RN 109971-63-3 CAPLUS

L24 ANSWER 149 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

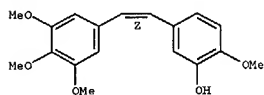
Double bond geometry as shown.



L24 ANSWER 150 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989;546274 CAPLUS  
 DOCUMENT NUMBER: 111:146274  
 TITLE: Structural and biochemical comparison of the antimitotic agents colchicine, combretastatin A4 and amphetamine  
 AUTHOR(S): McGown, A. T.; Fox, B. W.  
 CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp. Holt Radium Inst., Withington/Manchester, M20 9BX, UK  
 SOURCE: Anti-Cancer Drug Design (1989), 3(4), 249-54  
 CODEN: ACDDA; ISSN: 0266-9536  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The novel agents amphetamine and combretastatin A4 are shown to be very similar to colchicine in their interactions with purified tubulin. All 3 agents can inhibit tubulin assembly at similar treatment levels and have comparable affinity constants for tubulin. Amphetamine and combretastatin A4 are capable of displacing colchicine but not vinblastine from tubulin. A comparison of the structures of these agents shows that whereas colchicine and combretastatin A4 contain a trimethoxybenzene group (a moiety also found in other colchicine-like agents such as podophyllotoxins and steganacin) no obvious similarity is seen from amphetamine. The 3-dimensional structures of these agents, detd. from either crystallog. data or by energy minimization procedures, show, however, that all 3 agents consist of 2 planar, or almost planar, ring systems which are tilted with respect to each other. Using computer graphic techniques it can be shown that their ring systems are superimposable and that the planar sections of each mol. are at an angle of 50-60 degrees to each other. It is proposed that the angular bicyclic structure of these agents is one detg. factor for their efficient binding to tubulin.  
 IT 117048-59-6, NSC 817373  
 RL: BIOL (Biological study)  
 (tubulin binding by, structure in relation to)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

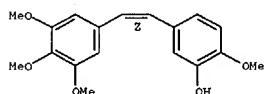
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L24 ANSWER 152 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989;417138 CAPLUS  
 DOCUMENT NUMBER: 111:17138  
 TITLE: Structural and biochemical comparison of the anti-mitotic agents colchicine, combretastatin A4 and amphetamine  
 AUTHOR(S): McGown, A. T.; Fox, B. W.  
 CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp., Withington/Manchester, M20 9BX, UK  
 SOURCE: Anti-Cancer Drug Design (1989), 3(4), 249-54  
 CODEN: ACDDA; ISSN: 0266-9536  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The novel agents amphetamine and combretastatin A4 were very similar to colchicine in their interactions with purified tubulin. All 3 agents inhibited tubulin assembly at similar treatment levels and had comparable affinity constants for tubulin. Amphetamine and combretastatin A4 were capable of displacing colchicine but not vinblastine from tubulin. A comparison of the structures of these agents showed that whereas colchicine and combretastatin A4 contain a trimethoxybenzene group (a moiety also found in other colchicine-like agents such as podophyllotoxins and steganacin) no obvious similarity was seen for amphetamine. The 3-dimensional structures of these agents, detd. from either crystallog. data or by energy minimization procedures, showed, however, that all 3 agents consist of 2 planar, or almost planar, ring systems which were tilted with respect to each other. Using computer graphic techniques it was shown that their ring system were superimposable and that the planar sections of each mol. were at an angle of 50-60 degrees to each other. Thus the angular bicyclic structure of these agents is one detg. factor for their efficient binding to tubulin.  
 IT 117048-59-6, NSC 817373  
 RL: BIOL (Biological study)  
 (tubulin assembly inhibition by, structure in relation to)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

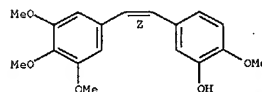
Double bond geometry as shown.



L24 ANSWER 151 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989;489891 CAPLUS  
 DOCUMENT NUMBER: 111:89891  
 TITLE: Antimitotic natural products combretastatin A-4 and combretastatin A-2: studies on the mechanism of their inhibition of the binding of colchicine to tubulin  
 AUTHOR(S): Lin, Chii M.; Ho, Holly H.; Pettit, George R.; Hamel, Ernest  
 CORPORATE SOURCE: Lab. Biochem. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA  
 SOURCE: Biochemistry (1989), 28(17), 6984-91  
 CODEN: BICHA; ISSN: 0006-2960  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

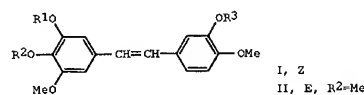
AB The mechanism of the binding of combretastatin A-4 (CS-A4) and combretastatin A-2 (CS-A2), isolated from Combretum cafrum, to tubulin was examd. indirectly by evaluating their effects on the binding of radiolabeled colchicine to the protein. There was rapid binding of both compds. to tubulin even at 0 degree. (binding was complete at the earliest times examd.), in contrast to the relatively slow and temp.-dependent binding of colchicine. Although the binding of the C. cafrum compds. to tubulin was quite tight, permitting ready isolation of near-stoichiometric amts. of drug-tubulin complex even in the absence of free drug, both CS-A4 and CS-A2 disocd. rapidly from tubulin in the presence of high concns. of radiolabeled colchicine. Apparent rate constants for drug disocn. from tubulin at 37 degree were 3.2 times 10^-3/s for CS-A4, 4.8 times 10^-3/s for CS-A2, and 2.9 times 10^-5/s for colchicine (half-lives of 3.6, 2.4, and 405 min, resp.). Thus, the effectiveness of the C. cafrum compds. as antimitotic agents appears to derive primarily from the rapidity of their binding to tubulin. A new model for the colchicine binding site on tubulin is proposed which envisages A-ring and C-ring subunits in homologous locations on the 2 tubulin subunits, with Ph rings binding as well as or better than the tropolone ring of colchicine in the C-ring subunit.  
 IT 117048-59-6, Combretastatin A4  
 RL: BIOL (Biological study)  
 (binding of, to tubulins, mechanism of)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

Double bond geometry as shown.



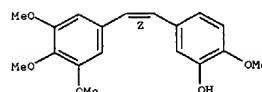
L24 ANSWER 153 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989;400276 CAPLUS  
 DOCUMENT NUMBER: 111:276  
 TITLE: Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4  
 AUTHOR(S): Pettit, G. R.; Singh, S. R.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D.  
 CORPORATE SOURCE: Cancer Res. Inst., Arizona State Univ., Tempe, AZ, 85287, USA  
 SOURCE: Experientia (1989), 45(2), 209-11  
 CODEN: EXPEAM; ISSN: 0014-4754  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

G1



AB From Combretum cafrum were isolated combretastatin A-4 (I, R1 = R2 = Me, R3 = H), combretastatin A-5 (I, R1 = H, R2 = R3 = Me), and combretastatin A-6 (II, R1 = H and R3 = Me) (the latter as the silyl ether). The structures of these compds. detd. by spectroscopic methods were confirmed by total syntheses. Combretastatins A-4, A-5 and A-6 were significantly active against murine L1210 and P388 lymphocytic leukemia cell lines with esp., combretastatin A-4 competing with combretastatin A-1 as the most inhibitor of colchicine binding to tubulin yet described. Combretastatin A-4 was an inhibitor of tubulin polymym.  
 IT 117048-59-6, Combretastatin A-4  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (of Combretum cafrum, as tubulin and neoplasm inhibitors, structure and synthesis of)  
 RN 117048-59-6 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

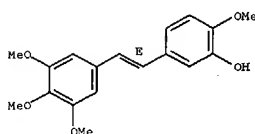
Double bond geometry as shown.



IT 117048-62-1  
 RL: BIOL (Biological study)  
 (of Combretum cafrum, structure of)  
 RN 117048-62-1 CAPLUS  
 CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (SCI) (CA INDEX NAME)

L24 ANSWER 153 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
INDEX NAME)

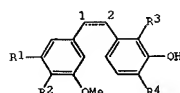
Double bond geometry as shown.



L24 ANSWER 154 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989:114573 CAPLUS  
 DOCUMENT NUMBER: 110:114573  
 TITLE: Isolation and synthesis of combretastatins as neoplasm inhibitors  
 INVENTOR(S): Pettit, George R.; Singh, Sheo Bux  
 PATENT ASSIGNEE(S): Arizona State University, USA  
 SOURCE: Eur. Pat. Appl., 31 pp.  
 CODEN: EFXADW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 276051	A2	19880727	EP 1988-300064	19880106
EP 276051	A3	19881130		
EP 276051	B1	19910821		
CA 1338645	A1	19961015	CA 1987-554733	19871217
JP 63233939	A2	19880929	JP 1987-327577	19871225
JP 2558131	B2	19961127		
AT 66452	E	19910915	AT 1988-300064	19880106
ES 2038747	T3	19930801	ES 1988-300064	19880106
US 5409953	A	19950425	US 1992-832998	19920210
US 5569786	A	19961029	US 1994-340156	19941115
PRIORITY APPL. INFO.:			US 1987-590	19870106
			EP 1988-300064	19880106
			US 1992-832998	19920210

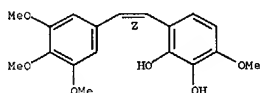
OTHER SOURCE(S): MARPAT 110:114573  
 GI



AB The title compds. (I; R1, R4 = OH, OMe; R2 = H, OMe; R3 = H, OH; R1R2 = OCH2O; 1,2-satd. or unsatd.) were synthesized and isolated from stem-wood of Combretum cafferum. 2,3,4-(HO)3C6H2CHO was added to aq. Na2B4O7 and, after 30 min stirring, NaOH and (MeO)2SO2 were added with stirring to give 2,3,4-(HO)2(MeO)C6H2CHO which was stirred 20 min with (Me3C)Me2SiCl in DMF contg. (Me2CH)2NEt to give 2,3,4-[(Me3C)Me2SiO]2(MeO)C6H2CHO. The latter was added to 3,4,5-(MeO)3C6H2COPh3 Br- (prepn. given) previously treated with BuLi in THF to give, after deprotection, I (R1 = R2 = R4 = OMe, R3 = OH) (II) which had ID50 of 2 .mu.M for inhibition of microtubule assembly in vitro. Capsules were prepd. contg. II 200, starch 20, talc 20, and Mg stearate 2 g per thousand.  
 IT 109971-63-3P 119307-36-7P  
 RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

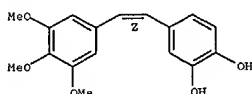
L24 ANSWER 154 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 (isolation and synthesis of, as neoplasm inhibitor)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]-  
 (9CI) (CA INDEX NAME)

Double bond geometry as shown.

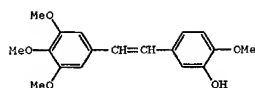


RN 119307-36-7 CAPLUS  
 CN 1,2-Benzenediol, 4-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

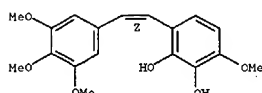


L24 ANSWER 155 OF 157 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1989:68959 CAPLUS  
 DOCUMENT NUMBER: 110:68959  
 TITLE: Interactions of tubulin with potent natural and synthetic analogs of the antimitotic agent combretastatin: a structure-activity study  
 AUTHOR(S): Lin, Chii M.; Singh, Sheo B.; Chu, Ping S.; Dempcy, Robert O.; Schmidt, Jean M.; Pettit, George R.; Hamel, Ernest  
 CORPORATE SOURCE: Lab. Pharmacol. and Exp. Therap., Natl. Cancer Inst., Bethesda, MD, 20892, USA  
 SOURCE: Molecular Pharmacology (1988), 34(2), 200-8  
 CODEN: MOPHA3; ISSN: 0026-895X  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB Available analogs (17 natural products and 22 synthetic agents) of combretastatin, an antineoplastic drug isolated from the bark of Combretum cafferum, were examd. for antimitotic and cytotoxic activity and for effects on tubulin polymn. and colchicine binding. Nineteen compds. inhibited cell growth by 50% or more at concns. of 1 .mu.M or less, and 14 inhibited tubulin polymn. by at least 50% at stoichiometric drug concns. The most potent cytotoxic agents strongly inhibited both tubulin polymn. and the binding of colchicine to tubulin. The most promising compd. is the (cis)-stilbene deriv. (cis)-1-(3,4,5-trimethoxyphenyl)-2-(3'-hydroxy-4'-methoxyphenyl)ethene (I), which has been named combretastatin A-4. This compd. inhibited cell growth by 50% at 7 nM, inhibited tubulin polymn. by 50% at 2.5 .mu.M (1/4 molar equivalent), and competitively inhibited colchicine binding with an apparent Ki of 0.14 .mu.M. The structure-activity relationship of these compds. is discussed.  
 IT 109971-63-3 117048-59-6 117048-62-1  
 RL: PRP (Properties)  
 (antitumor and antimitotic and tubulin polymn.-inhibiting and colchicine binding-inhibiting effects of, structure in relation to)  
 RN 109971-63-3 CAPLUS  
 CN 1,2-Benzenediol, 3-methoxy-6-[(12)-2-(3,4,5-trimethoxyphenyl)ethenyl]-  
 (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS

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=> log y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	735.35	1189.14
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-104.16	-106.11

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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
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NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
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NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEx enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY

NEWS 30 Apr 11 Display formats in DGENE enhanced  
NEWS 31 Apr 14 MEDLINE Reload  
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced  
NEWS 33 Jun 13 Indexing from 1947 to 1956 added to records in CA/CAPLUS  
NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in  
WPIDS/WPINDEX/WPIX  
NEWS 35 Apr 28 RDISCLOSURE now available on STN  
NEWS 36 May 05 Pharmacokinetic information and systematic chemical names  
added to PHAR  
NEWS 37 May 15 MEDLINE file segment of TOXCENTER reloaded  
NEWS 38 May 15 Supporter information for ENCOMPAT and ENCOMPLIT updated  
NEWS 39 May 16 CHEMREACT will be removed from STN  
NEWS 40 May 19 Simultaneous left and right truncation added to WSCA  
NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and  
right truncation  
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB  
NEWS 43 Jun 06 PASCAL enhanced with additional data  
  
NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6  
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

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PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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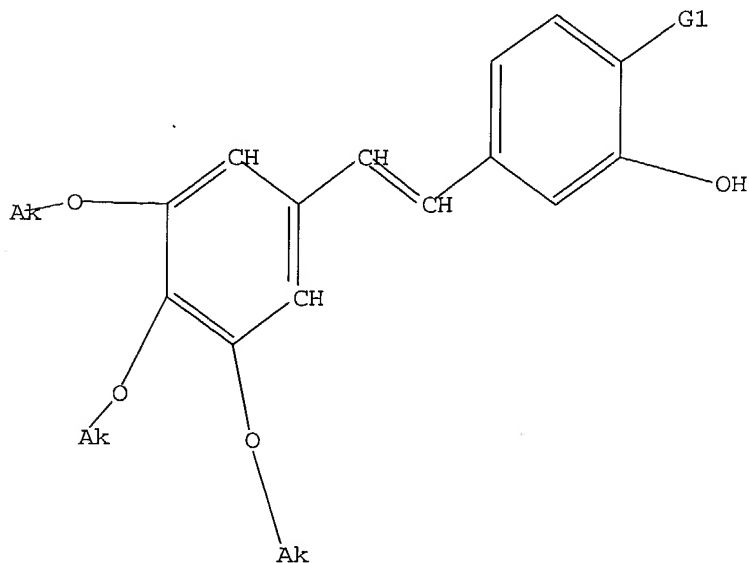
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L1 STRUCTURE UPLOADED

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L1 HAS NO ANSWERS

L1 STR



G1 C,S,X

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SAMPLE SCREEN SEARCH COMPLETED - 22 TO ITERATE

100.0% PROCESSED 22 ITERATIONS 2 ANSWERS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 159 TO 721  
PROJECTED ANSWERS: 2 TO 124

L2 2 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED - 381 TO ITERATE

100.0% PROCESSED 381 ITERATIONS 12 ANSWERS  
SEARCH TIME: 00.00.01

L3 12 SEA SSS FUL L1

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FULL ESTIMATED COST	148.15	148.57

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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25  
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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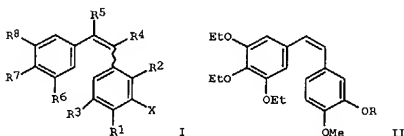


L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:487508 CAPLUS  
 DOCUMENT NUMBER: 137:47052  
 TITLE: Preparation of substituted stilbenes as antitumor agents  
 INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hopworth, Lucy Annette; Butler, John  
 PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK  
 SOURCE: PCT Int. Appl., 76 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		

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OTHER SOURCE(S): MARPAT 137:47052  
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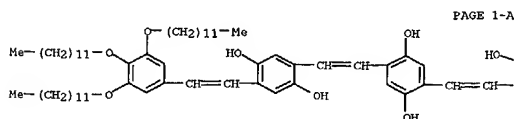


AB Stilbene and quinone compds. related to combretastatin A-4, such as I (X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3, halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR; R6, R7, R8 = H, alkyl, alkoxy; zigzag bond

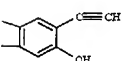
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:81725 CAPLUS  
 DOCUMENT NUMBER: 136:410547  
 TITLE: Metallo-supramolecular oligo(p-phenylene vinylene)/[60]fullerene architectures: towards functional materials  
 AUTHOR(S): El-Ghayoury, Abdelkrim; Schenning, Albertus P. H. J.; van Hal, Paul A.; Weidl, Christian K.; van Dongen, Joost L. J.; Janssen, Rene A. J.; Schubert, Ulrich S.; Meijer, E. W.  
 CORPORATE SOURCE: Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, Eindhoven, 5600 MB, Neth.  
 SOURCE: Thin Solid Films (2002), 403-404, 97-101  
 CODEN: THSFAP; ISSN: 0040-6090  
 PUBLISHER: Elsevier Science S.A.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The assembly of pi-conjugated [oligo(p-phenylene vinylene)] (OPV) donors and [60]fullerene acceptor moieties into a supramol. donor-acceptor system is achieved by Ru complexation. The synthesis and optical properties of a novel photoactive supramol. dyad and triad are described to access the photoinduced formation of a charge-sepd. state.

IT 429688-40-4  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (for prepn. of ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)  
 RN 429688-40-4 CAPLUS  
 CN 1,4-Benzenediol, 2-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-5-[2-(4-ethynyl-2,5-dihydroxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



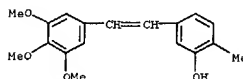
PAGE 1-A



PAGE 1-B

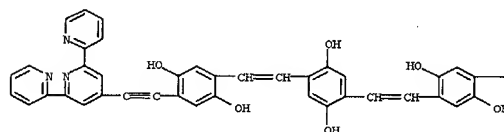
IT 429688-35-7DP, substituted  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (for prepn. of ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)  
 RN 429688-35-7 CAPLUS  
 CN 1,4-Benzenediol, 2-[2-[2,5-dihydroxy-4-[(2,2',6',2''-terpyridin)-4'-yl-kappa.N1, kappa.N1', kappa.N1'']oxy]pentyl]naphtho[2',3':1,9][5,6]fullerene-C60-1h-6'-carboxamide]-[2-[2-[2,5-dihydroxy-4-[(2,2',6',2''-terpyridin)-4'-yl-kappa.N1, kappa.N1', kappa.N1'']ethynyl]phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-1,4-benzenediol]-, (OC-6-23)-, bis[tetrafluoroborate(1-)] (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 = cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butylidimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBSMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.  
 IT 436534-68-0p  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of substituted stilbenes as antitumor agents)  
 RN 436534-68-0 CAPLUS  
 CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

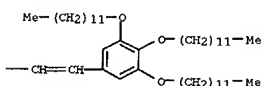


L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)  
 y[ethynyl]phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

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PAGE 1-B



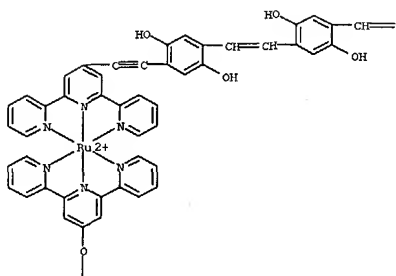
IT 429688-39-1DP, substituted  
 RL: FRP (Properties); SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and photoinduced charge sepn. in ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)  
 RN 429688-39-1 CAPLUS  
 CN Ruthenium(2+), [1',4'-dihydro-N-{5-[(2,2',6',2''-terpyridin)-4'-yl-kappa.N1, kappa.N1', kappa.N1'']oxy]pentyl]naphtho[2',3':1,9][5,6]fullerene-C60-1h-6'-carboxamide]-[2-[2-[2,5-dihydroxy-4-[(2,2',6',2''-terpyridin)-4'-yl-kappa.N1, kappa.N1', kappa.N1'']ethynyl]phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-1,4-benzenediol]-, (OC-6-23)-, bis[tetrafluoroborate(1-)] (9CI) (CA INDEX NAME)

CM 1

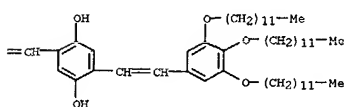
CRN 429688-38-0  
 CMF C172 H133 N7 O11 Ru  
 CCI CCS

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A

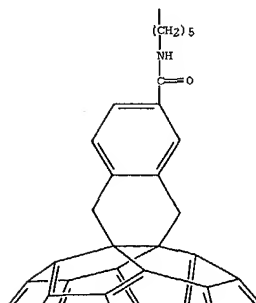


PAGE 1-B

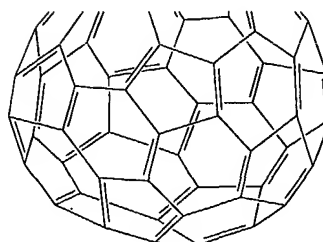


L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 2-A



PAGE 3-A



CM 2  
CRN 14874-70-5  
CMF B F4  
CCI CCS

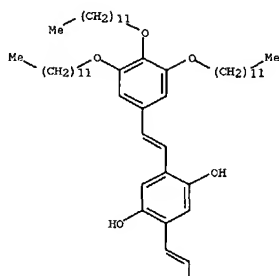
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 429698-37-9DF, substituted  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of)  
RN 429698-37-9 CAPLUS  
CN Ruthenium(2+), bis[2-[2-(2,5-dihydroxy-4-[[[2,2':6',2''-terpyridin]-4'-yl-  
.kappa.N1',.kappa.N1'',.kappa.N1''')ethynyl]phenyl]ethenyl]-5-[2-[2,5-  
dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-1,4-  
benzenediol]-, (OC-6-1'2)-, bis[tetrafluoroborate(1-)] (SCI) (CA INDEX  
NAME)

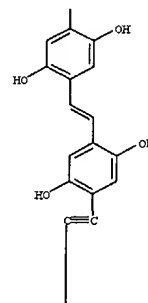
CM 1  
CRN 429698-36-8  
CMF C166 H210 N6 O18 Ru  
CCI CCS

PAGE 1-A

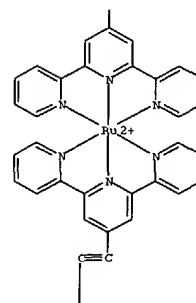


L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 2-A

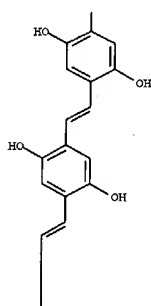


PAGE 3-A

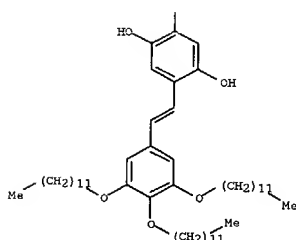


L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

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PAGE 5-A



CM 2

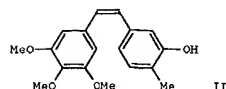
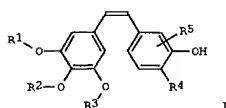
CRN 14874-70-5  
CMF B P4

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:137169 CAPLUS  
DOCUMENT NUMBER: 134:178403  
TITLE: Preparation and use of cis-stilbenes with vascular damaging activity  
INVENTOR(S): Davis, Peter David  
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK  
SOURCE: PCT Int. Appl., 17 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GE, GD, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TH, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TN  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
EP 1206429 A2 20020522 EP 2000-951727 20000809  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LT, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL  
JP 2003507356 T2 20030225 JP 2001-516880 20000809  
PRIORITY APPLN. INFO.: GB 1999-18912 A 19990812  
WO 2000-GB3067 W 20000809  
OTHER SOURCE(S): MANPAT 134:178403  
GI



AB Comps. of formula I (wherein: R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

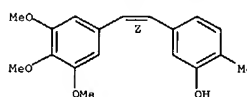
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)



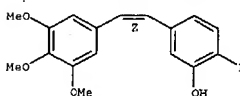
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester produg. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butyl-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyl ether intermediate provided II as a white solid. Comps. I showed activity against tumor vasculature measured by reduct. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These comps. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.  
IT 288585-59-1P, (2)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
RN 288585-59-1 CAPLUS  
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
Double bond geometry as shown.

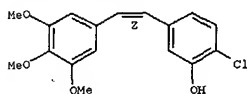


IT 326850-81-1P, (2)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-82-2P, (2)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene 326850-83-3P, (2)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
RN 326850-81-1 CAPLUS  
CN Phenol, 2-fluoro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)  
Double bond geometry as shown.



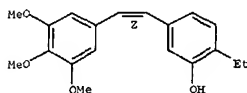
RN 326850-82-2 CAPLUS  
CN Phenol, 2-chloro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)  
Double bond geometry as shown.

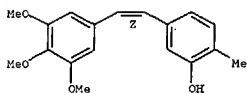


RN 326850-83-3 CAPLUS  
CN Phenol, 2-ethyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:592548 CAPLUS  
DOCUMENT NUMBER: 133:177486  
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity  
INVENTOR(S): Davis, Peter David  
PATENT ASSIGNER(S): Angiogene Pharmaceuticals Ltd., UK  
SOURCE: PCT Int. Appl., 31 pp.  
CODEN: FIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W:				
AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
HW:				
GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPLN. INFO.:			GB 1999-3403	A 19990216
			WO 2000-GB503	W 20000215

OTHER SOURCE(S): MARPAT 133:177486  
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (2)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyl)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (2)-1-(4-methoxy-3-NG-nitroarginyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/Kg i.p. in mice bearing CaNT or SAs tumors gave 95% reduct. in vascular vol. and 91-100% tumor necrosis.  
IT 285585-59-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of substituted stilbene compds. with vascular damaging activity)  
RN 285585-59-1 CAPLUS  
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

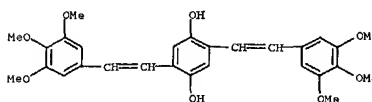
Double bond geometry as shown.

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:351266 CAPLUS  
DOCUMENT NUMBER: 132:345122  
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors  
INVENTOR(S): Huyberechts, Guido; Jordens, Sven  
PATENT ASSIGNER(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instituut Antwerpen  
SOURCE: Eur. Pat. Appl., 18 pp.  
CODEN: EFXKDW  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1998-870254	19981117
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			EP 1998-870254	A 19981117
			US 1999-122211P	P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.  
IT 270069-97-1DP, alkyl derive.  
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)  
RN 270069-97-1 CAPLUS  
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:351265 CAPLUS

DOCUMENT NUMBER: 132:345121

TITLE: Sensor comprising an oligomer binding layer and method

of making such sensor and arrays of such sensors

INVENTOR(S): Huyberechts, Guido; Jordens, Sven

PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw,

Belg.; Universitaire Instelling Antwerpen

SOURCE: Eur. Pat. Appl., 14 pp.

CODEN: EPXADW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

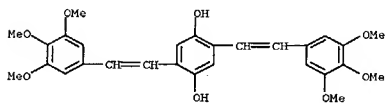
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002048751	A1	20020425	US 1999-441118	19991117
PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117				
US 1999-122211P P 19990301				

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT 270069-97-IDP, alkyl derivs.  
KL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)

RN 270069-97-1 CAPLUS  
CN 1,4-Benzenedial, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> log y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

28.47

177.04

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-3.91

-3.91

STN INTERNATIONAL LOGOFF AT 08:46:31 ON 19 JUN 2003